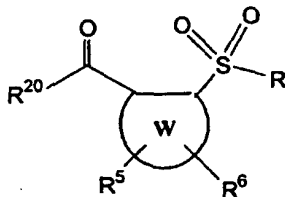


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<b>(21) International Application Number:</b> PCT/US00/06713  <b>(22) International Filing Date:</b> 12 May 2000 (12.05.00)  <b>(30) Priority Data:</b> 09/310,813 12 May 1999 (12.05.99) US  <b>(71) Applicant (for all designated States except US):</b> G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BEDELL, Louis, J. [US/US]; 1832 E. Camp McDonald Road, Mt. Prospect, IL 60056 (US). MCDONALD, Joseph, J. [US/US]; 1036 Johanna Drive, Ballwin, MO 63021 (US). BARTA, Thomas, E. [US/US]; 1133 Maple Avenue, #3W, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1800 Maplewood Lane, Glenview, IL 60025 (US). RAO, Shashidhar, N. [IN/US]; 736 Bellerive Manor Drive, St. Louis, MO 63141 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). MISCHKE, Brent, V. [US/US]; 25 White River Lane, Defiance, MO 63341 (US). GETMAN, Daniel,	P. [US/US]; 66 Sunny Hill Court, Chesterfield, MO 63017 (US). DECRESCENZO, Gary, A. [US/US]; 7345 Spruce Hill Court, St. Charles, MO 63304 (US). VILLAMIL, Clara, I. [US/US]; 813 Long Road, Glenview, IL 60025 (US).  <b>(74) Agents:</b> WARNER, James, W. et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).  <b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

**(54) Title:** HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEASE INHIBITORS

(a)

**(57) Abstract**

A sulfonyl aromatic or heteroaromatic ring hydroxamic acid compound that *inter alia* inhibits matrix metalloprotease activity is disclosed as a treatment process that comprises administering a contemplated sulfonyl aromatic or heteroaromatic ring hydroxamic acid compound in an MMP enzyme-inhibiting effective amount to a host having a condition associated with pathological matrix metalloprotease activity. A contemplated compound corresponds in structure to formula (a) wherein W and the R groups are defined elsewhere.

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## HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEASE INHIBITORS

### Description

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#### Technical Field

This invention is directed to proteinase (protease) inhibitors, and more particularly to sulfonyl aryl or heteroaryl hydroxamic acid compounds that, *inter alia*, inhibit the activity of matrix metalloproteinases, compositions of those inhibitors, intermediates for the syntheses of those compounds, processes for the preparation of the compounds and processes for treating pathological conditions associated with pathological matrix metalloproteinase activity.

#### Background of the Invention

Connective tissue, extracellular matrix constituents and basement membranes are required components of all mammals. These components are the biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, elastin, proteoglycans, fibronectin and laminin. These biochemicals make up, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor.

Under normal conditions, connective tissue turnover and/or repair processes are

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controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states. Inhibition of the enzymes responsible for the loss of equilibrium provides a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases, or MMPs).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many



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pathological conditions. Examples include  
rheumatoid arthritis, osteoarthritis, septic  
arthritis; corneal, epidermal or gastric  
ulceration; tumor metastasis, invasion or  
5 angiogenesis; periodontal disease; proteinuria;  
Alzheimer's Disease; coronary thrombosis and bone  
disease. Defective injury repair processes can  
also occur. This can produce improper wound  
healing leading to weak repairs, adhesions and  
10 scarring. These latter defects can lead to  
disfigurement and/or permanent disabilities as with  
post-surgical adhesions.

Matrix metalloproteases are also involved  
in the biosynthesis of tumor necrosis factor (TNF)  
15 and inhibition of the production or action of TNF  
and related compounds is an important clinical  
disease treatment mechanism. TNF- $\alpha$ , for example,  
is a cytokine that at present is thought to be  
produced initially as a 28 kD cell-associated  
20 molecule. It is released as an active, 17 kD form  
that can mediate a large number of deleterious  
effects *in vitro* and *in vivo*. For example, TNF can  
cause and/or contribute to the effects of  
inflammation, rheumatoid arthritis, autoimmune  
25 disease, multiple sclerosis, graft rejection,  
fibrotic disease, cancer, infectious diseases,  
malaria, mycobacterial infection, meningitis,  
fever, psoriasis, cardiovascular/pulmonary effects  
such as post-ischemic reperfusion injury,  
30 congestive heart failure, hemorrhage, coagulation,  
hyperoxic alveolar injury, radiation damage and  
acute phase responses like those seen with  
infections and sepsis and during shock such as

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septic shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF- $\alpha$  convertase is a metalloproteinase  
5 involved in the formation of active TNF- $\alpha$ .  
Inhibition of TNF- $\alpha$  convertase inhibits production of active TNF- $\alpha$ . Compounds that inhibit both MMPs activity have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO  
10 97/20824. There remains a need for effective MMP and TNF- $\alpha$  convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557  
15 (1994), McGeehan et al., *Nature* 376, 558-561 (1994)).

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine  
20 involution, possibly implantation, cleavage of APP ( $\beta$ -Amyloid Precursor Protein) to the amyloid plaque and inactivation of  $\alpha_1$ -protease inhibitor ( $\alpha_1$ -PI).  
Inhibition of these metalloproteases permits the control of fertility and the treatment or  
25 prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as  $\alpha_1$ -PI  
supports the treatment and prevention of diseases  
30 such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

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Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin (MMP-3), gelatinase (MMP-2), gelatinase B (MMP-9) or collagenase III (MMP-13) may be relatively more important than inhibition of collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation in inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97:2011-2019 (1996).

Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP),  $\alpha_2$ -macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases. A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the production of angiotensin II, a potent pressor substance in

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mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO95/12389, WO96/11209 and U.S. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem.*, 29:271-334 (1992) and those of Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997) and Denis et al., *Invest. New Drugs*, 15(3): 175-185 (1997).

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC<sub>50</sub> values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC<sub>50</sub> value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997).

Meta analysis of data from Phase I/II studies using marimastat in patients with advanced,

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rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although marimastat exhibited some measure of efficacy via these markers, toxic side effects were noted. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

In view of the importance of hydroxamate MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs in clinical trials, it would be a great benefit if hydroxamates of greater enzyme specificity could be found. This would be particularly the case if the hydroxamate inhibitors exhibited strong inhibitory activity against one or more of MMP-2, MMP-9 or MMP-13 that are associated with several pathological conditions, while at the same time exhibiting limited inhibition of MMP-1, an enzyme that is relatively ubiquitous and as yet not associated with any pathological condition. The disclosure that follows describes one family of

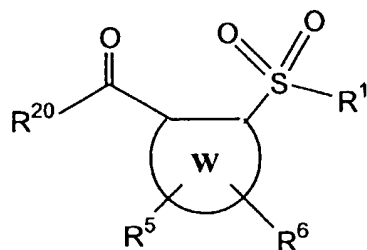
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hydroxamate MMP inhibitors that exhibit those desirable activities

Brief Summary of the Invention

5           The present invention is directed to a family of molecules that among other properties inhibit matrix metalloprotease (MMP) activity and particularly inhibit the activity of one or more of MMP-2, MMP-9, or MMP-13, while generally exhibiting  
10 little activity against MMP-1. The present invention is also directed to intermediates useful in the synthesis of inhibitors, processes for preparing a contemplated compound and for treating a mammal having a condition associated with  
15 pathological matrix metalloprotease activity.

Briefly, one embodiment of the present invention is directed to a sulfonyl aryl or heteroaryl hydroxamic acid compound, or a pharmaceutically acceptable salt of such a compound  
20 that can act as a matrix metalloprotease enzyme inhibitor, a precursor to such a compound or a pro-drug form of such a compound. A contemplated compound corresponds in structure to Formula C.



C

25

wherein

the ring structure W is a 5- or 6-membered aromatic or heteroaromatic ring;

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R<sup>1</sup> is (i) a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO<sub>2</sub>-group and having a length greater than about that of a hexyl group and less than about that of an eicosyl group, said R<sup>1</sup> defining a three-dimensional volume, when rotated about an axis drawn through the SO<sub>2</sub>-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO<sub>2</sub>-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings. Alternatively, R<sup>1</sup> is an -NR<sup>7</sup>R<sup>8</sup> group in which R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrido, hydrocarbyl, aryl, substituted aryl, arylhydrocarbyl, and substituted arylhydrocarbyl. More preferably, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, R<sup>a</sup>oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and a heterocyclo substituent, each of which substituent groups is optionally substituted with an -A-R-E-Y substituent;

in such an -A-R-E-Y substituent, A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;

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- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- 5 (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- 10 (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded
- 15 to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;
- the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl,
- 20 heterocycloalkoxyalkyl, aryloxyalkyl, heteroarylthioalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl
- 25 substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl,
- 30 alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy,



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hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the group E is selected from the group consisting of

- 5 (1)  $-\text{COR}^g-$  or  $-\text{R}^g\text{CO}-$ ;  
(2)  $-\text{CON}(\text{R}^k)-$  or  $-(\text{R}^k)\text{NCO}-$ ;  
(3)  $-\text{CO}-$ ;  
(4)  $-\text{SO}_2\text{R}^g-$  or  $-\text{R}^g\text{SO}_2-$ ;  
(5)  $-\text{SO}_2-$ ;  
10 (6)  $-\text{N}(\text{R}^k)-\text{SO}_2-$  or  $-\text{SO}_2-\text{N}(\text{R}^k)-$ ; or  
(7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy,  
15 haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl,  $\text{R}^a\text{oxyalkyl}$ , perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
20 cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl, aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group  
25 consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, perfluoroalkyl, perfluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently  
30 selected from hydrido, alkyl, and an aralkyl group;  
or

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$R^7$  and  $R^8$  taken together with the nitrogen atom to which they are bonded form a group -G-A-R-E-Y wherein

G is a N-heterocyclo group;

5 the substituent A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- 10 (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- 15 (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>) - or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- 20 (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- 25 (18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, 30 heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a

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heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, 5 perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, 10 hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the moiety E is selected from the group consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- 15 (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>G</sup>- or -R<sup>G</sup>-SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- 20 (7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, 25 hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a 30 aminoalkyl group, wherein the aryl, heteroaryl, aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two

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radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, perfluoroalkyl, perfluoroalkoxy and an amino group  
5 wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

Alternatively, and still more preferably,  $R^7$  and  $R^8$  taken together with the nitrogen atom to which  
10 they are bonded; i.e., a  $-NR^7R^8$  group, form a group -G-A-R-E-Y wherein

G is a N-heterocyclo group;

the substituent A is selected from the group consisting of

- 15 (1) -O-;
- (2) -S-;
- (3)  $-NR^k-$ ;
- (4)  $-CO-N(R^k)$  or  $-N(R^k)-CO-$ ;
- (5)  $-CO-O-$  or  $-O-CO-$ ;
- 20 (6)  $-O-CO-O-$ ;
- (7)  $-HC=CH-$ ;
- (8)  $-NH-CO-NH-$ ;
- (9)  $-C\equiv C-$ ;
- (10)  $-N=N-$ ;
- 25 (11)  $-NH-NH-$ ;
- (12)  $-CS-N(R^k)-$  or  $-N(R^k)-CS-$ ;
- (13)  $-CH_2-$ ;
- (14)  $-O-CH_2-$  or  $-CH_2-O-$ ;
- (15)  $-S-CH_2-$  or  $-CH_2-S-$ ;
- 30 (16)  $-SO-$ ; and
- (17)  $-SO_2-$ ; or

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(18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the moiety E is selected from the group consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>G</sup>- or -R<sup>G</sup>-SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy,

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haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
5 trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
10 radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
15 (ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group.

Substituents R<sup>5</sup> and R<sup>6</sup> are independently  
selected from the group consisting of a hydrido,  
alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl,  
20 cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl,  
a R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol (-SH), alkylthio,  
arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy,  
perfluoroalkyl, haloalkyl, heterocycloxy and a  
R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

25 or R<sup>5</sup> and R<sup>6</sup> together with the atoms to  
which they are bonded form a further aliphatic or  
aromatic carbocyclic or heterocyclic ring having 5-  
to 7-members.

A R<sup>20</sup> group is (a) -O-R<sup>21</sup>, where R<sup>21</sup> is selected  
30 from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl,  
aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group and a pharmaceutically  
acceptable cation, (b) -NR<sup>13</sup>-O-R<sup>22</sup> wherein R<sup>22</sup> is a

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selectively removable protecting group such as a 2-tetrahydropyranyl, benzyl, p-methoxybenzyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, trisubstituted silyl group or o-nitrophenyl group, peptide synthesis resin and the like, wherein the trisubstituted silyl group is substituted with C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, or ar-C<sub>1</sub>-C<sub>6</sub>-alkyl or a mixture thereof, and R<sup>13</sup> is a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl or benzyl group, (c) -NR<sup>13</sup>-O-R<sup>14</sup>, where R<sup>13</sup> is as before and R<sup>14</sup> is hydrido, a pharmaceutically acceptable cation or C(V)R<sup>15</sup> where V is O (oxo) or S (thioxo) and R<sup>15</sup> is selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, aryloxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, heteroaryl and amino C<sub>1</sub>-C<sub>6</sub>-alkyl group wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, and C<sub>1</sub>-C<sub>6</sub>-alkanoyl radical, or (iii) wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) -NR<sup>23</sup>R<sup>24</sup>, where R<sup>23</sup> and R<sup>24</sup> are independently selected from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, amino C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, and an ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group, or R<sup>23</sup> and R<sup>24</sup> together with the depicted nitrogen atom form a 5- to 8-membered ring

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containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur.

In the formula above,  $R^a$  is selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, 5 arylalkylcarbonyl,  $R^bR^c$ aminoalkanoyl, haloalkanoyl,  $R^bR^c$ aminoalkyl, alkoxyalkyl, haloalkyl and an arylalkyloxy group;

$R^b$  and  $R^c$  are independently selected from 10 the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, 15 heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, 20 alkoxyalkylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl, 25 thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkyl, aryloxyalkyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, aminosulfonyl wherein the amino nitrogen is (i) unsubstituted or (ii) independently substituted with 30 one or two  $R^d$  radicals, or the substituents on the amino group taken together with the amino nitrogen form a saturated or partially unsaturated heterocyclo group optionally substituted with one, two or three



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groups independently selected from  $R^d$  substituents or a heteroaryl group optionally substituted with one, two or three groups independently selected from  $R^f$  substituents;

5  $R^d$  and  $R^e$  are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl, alkoxycarbonyl or arylalkyloxycarbonyl group;

10  $R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen (halo; F, Cl, Br, I), aryl, alkoxy, cyano, and  $R^dR^e$ amino group;

$R^g$  is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, 15 alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  $R^hR^i$ -amino, 20 alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, 25 carboxy,  $R^hR^i$ -aminocarbonyloxy,  $R^hR^i$ -aminocarbonyl,  $R^hR^i$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^hR^i$ -aminosulfonyl,  $R^hR^i$ -aminocarbonyl( $R^h$ )amino, trifluoromethylsulfonyl( $R^h$ )amino, heteroarylsulfonyl- ( $R^h$ )amino, arylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )- 30 aminocarbonyl, alkylsulfonyl( $R^h$ )amino, arylcarbonyl-

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(R<sup>h</sup>)aminosulfonyl, and an alkylsulfonyl(R<sup>h</sup>) - aminocarbonyl substituent;

R<sup>h</sup> is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is optionally substituted by one or two groups independently selected from R<sup>j</sup> substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

R<sup>i</sup> is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two R<sup>j</sup> substituents;

R<sup>j</sup> is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group; wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl

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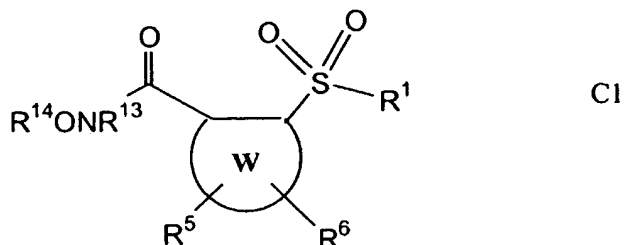
groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

5  $R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,  $R^C R^d$  amino carbonyl,  $R^C R^d$  aminosulfonyl,  $R^C R^d$  aminoalkanoyl and  $R^C R^d$  aminoalkysulfonyl.

10 In some preferred embodiments,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrido, hydrocarbyl, preferably  $C_1-C_4$  hydrocarbyl, hydroxylhydrocarbyl, hydroxyl, amino, dihydrocarbylamino, heterocyclo,  
15 heterocyclohydrocarbyl, heterocyclooxy, and heterocyclothio.

In preferred embodiments, the 5- or 6-membered aromatic or heteroaromatic ring W is a 1,2-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 4,5-pyridinylene, 2,3-pyrazinylene, 4,5-pyrimidinylene,  
20 or 5,6-pyrimidinylene group.

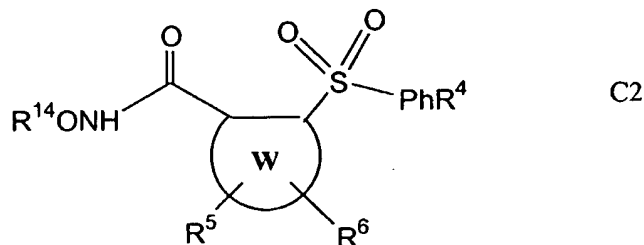
In some preferred embodiments,  $R^{20}$  is  $-NR^{13}-O-R^{14}$ , whereas in other preferred embodiments,  $R^{20}$  is  $-NR^{13}-O-R^{22}$ . In particularly preferred  
25 embodiements,  $R^{20}$  is  $-NHOH$  so that a compound of Formula C corresponds in structure to Formula C1



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wherein W, R<sup>1</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined before.

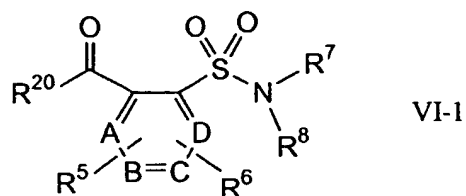
In one preferred embodiment, a contemplated  
5 compound corresponds in structure to Formula C2,



wherein W, R<sup>5</sup>, R<sup>6</sup> and R<sup>14</sup> are as defined above and Ph is a phenyl group substituted at the 4-position with substituent R<sup>4</sup>. A R<sup>4</sup> substituent can  
10 be a single-ringed cyclohydrocarbyl, heterocyclo, aryl such as phenyl or heteroaryl group or another substituent having a chain length of 3 to about 14 carbon atoms such as a hydrocarbyl or hydrocarbyloxy group [e.g., C<sub>3</sub>-C<sub>14</sub> hydrocarbyl or O-C<sub>2</sub>-C<sub>14</sub>  
15 hydrocarbyl], a phenoxy group [-OC<sub>6</sub>H<sub>5</sub>], a thiophenoxy group [phenylsulfanyl; -SC<sub>6</sub>H<sub>5</sub>], an anilino group [-NHC<sub>6</sub>H<sub>5</sub>], a phenylazo group [-N<sub>2</sub>C<sub>6</sub>H<sub>5</sub>], a phenylureido group [aniline carbonylamino; -NHC(O)NH-C<sub>6</sub>H<sub>5</sub>], a benzamido group [-NHC(O)C<sub>6</sub>H<sub>5</sub>], a  
20 nicotinamido group [3-NHC(O)C<sub>5</sub>H<sub>4</sub>N], an isonicotinamido group [4-NHC(O)C<sub>5</sub>H<sub>4</sub>N], or a picolinamido group [2-NHC(O)C<sub>5</sub>H<sub>4</sub>N]. A R<sup>4</sup> substituent is further defined hereinafter.

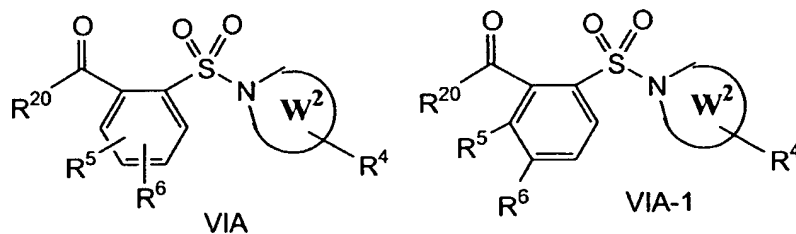
In another aspect of the invention, a  
25 contemplated compound corresponds in structure to Formula VI-1

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wherein each of  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^{20}$  is as defined before and each of A, B, C and D is carbon, nitrogen, sulfur or oxygen and is present or absent so that the depicted ring has 5- or 6-members. When  $R^{20}$  is NH-OH, compound of one of the above formulas such as Formula C or C1 is a hydroxamate that is a selective inhibitor of MMP-2 over MMP-1 and usually also over MMP-13. That is, a hydroxamate compound of one of the formulas such as Formula C or C1 exhibits greater activity in inhibiting MMP-2 than in inhibiting MMP-1 and usually also MMP-13. When  $R^{20}$  is other than NH-OH, a compound of Formula VI-1 can be a precursor, pro-drug or active carboxylate as is the compound of Example 13.

A particularly preferred embodiment of this aspect is a compound that corresponds in structure to Formulas VIA or VIA-1



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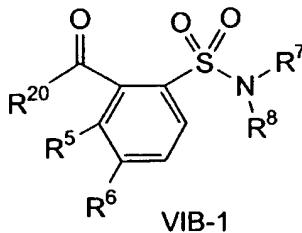
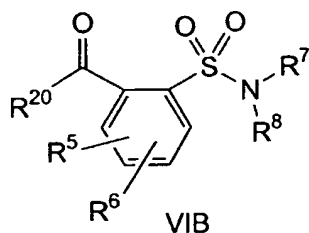
wherein  $R^{20}$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined before and ring structure  $W^2$  including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 6-members, and  $R^4$  is bonded at the 4-position

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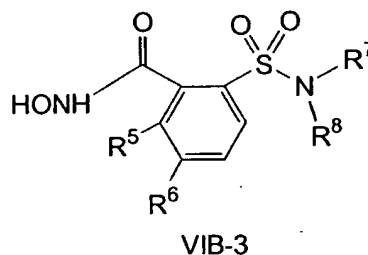
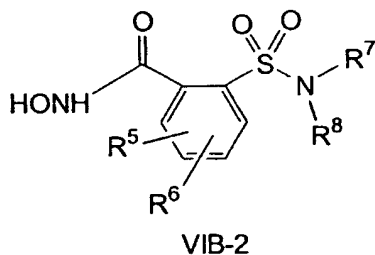
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relative to that depicted nitrogen atom when  $W^2$  is a 6-membered ring and at the 3- or 4-position relative to that depicted nitrogen when  $W^2$  is a 5-membered ring.

- 5                    Another particularly preferred embodiment of this aspect is a compound that corresponds in structure to Formulas VIB, VIB-1, VIB-2 or VIB-3

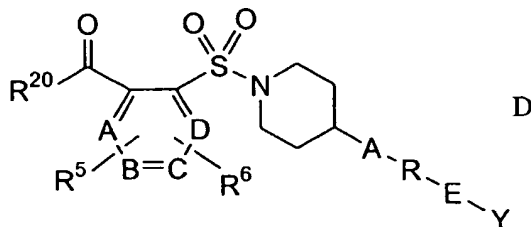


10



wherein  $R^{20}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are as defined before.

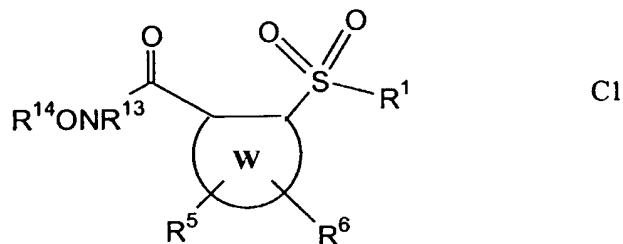
- 15                    A particularly preferred group of compounds of this class are the compounds whose structure corresponds to Formula D



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wherein the substituent groups or moieties A, R, E, Y, R<sup>20</sup>, R<sup>5</sup> and R<sup>6</sup> are as before described.

A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity is also contemplated. That process comprises administering to a mammalian host having such a condition a compound corresponding in structure to Formula C, such as a compound corresponding in structure to Formula C1, below, or a salt of such a compound, that selectively inhibits one or more MMPs, while exhibiting less activity against at least MMP-1 in an MMP enzyme-inhibiting effective amount. A contemplated compound also does not substantially inhibit the production of TNF.



15

wherein W, R<sup>1</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined before.

Among the several benefits and advantages of the present invention are the provision of compounds and compositions that are effective for the inhibition of metalloproteinases implicated in diseases and disorders involving uncontrolled breakdown of connective tissue.

More particularly, a benefit of this invention is the provision of a compound and composition effective for inhibiting metalloproteinases, particularly MMP-13 and/or MMP-2, associated with pathological conditions such as, for

25

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example, rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulceration, tumor metastasis, invasion or angiogenesis, periodontal disease, proteinuria, Alzheimer's  
5 Disease, coronary thrombosis, plaque formation and bone disease.

An advantage of the invention is the provision of a method for preparing such compounds and compositions. Another benefit is the provision  
10 of a method for treating a pathological condition associated with abnormal matrix metalloproteinase activity.

Another advantage of the invention is the provision of compounds, compositions and methods  
15 effective for treating such pathological conditions by selective inhibition of a metalloproteinase such as MMP-13 and MMP-2 associated with such conditions with minimal side effects resulting from inhibition of other proteinases such as MMP-1, whose activity is  
20 necessary or desirable for normal body function.

Still further benefits and advantages of the invention will be apparent to the skilled worker from the disclosure that follows.

#### 25 Detailed Description of Preferred Embodiments

In accordance with the present invention, it has been found that certain sulfonyl aryl or heteroaryl hydroxamic acids (hydroxamates) are effective, *inter alia*, for inhibition of matrix  
30 metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain sulfonyl aryl or heteroaryl



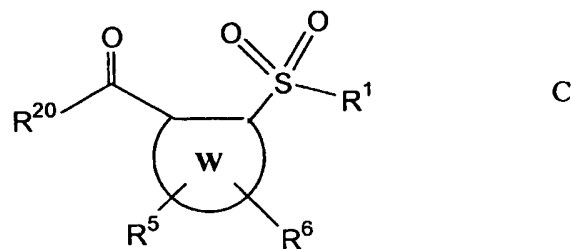
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hydroxamic acid compounds are effective for inhibition of collagenase III (MMP-13) and also gelatinase A (MMP-2), which can be particularly destructive to tissue if present or generated in  
5 abnormal quantities or concentrations, and thus exhibit a pathological activity.

Moreover, it has been discovered that many of these aromatic sulfonyl alpha-cycloamino hydroxamic acids are selective in the inhibition of  
10 MMPs associated with diseased conditions without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that particularly preferred sulfonyl aryl or heteroaryl  
15 hydroxamic acid compounds or salts of such compounds are particularly active in inhibiting of MMP-13 and/or MMP-2, while having a limited or minimal effect on MMP-1, and some compounds such as that of Example 8, also exhibit minimal inhibition of MMP-7.  
20 This point is discussed in detail hereinafter and is illustrated in the Inhibition Table hereinafter.

One embodiment of the present invention is directed to a sulfonyl aryl or heteroaryl hydroxamic acid compound, a pharmaceutically  
25 acceptable salt of such a compound that can act as a matrix metalloprotease enzyme inhibitor, a precursor to such a compound or a pro-drug form of such a compound. A contemplated compound corresponds in structure to Formula C.

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wherein

the ring structure W is a 5- or 6-membered aromatic or heteroaromatic ring;

- 5  $R^1$  is (i) a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted  $SO_2$ -group and having a length greater than about that of a hexyl group and less than about that of an
- 10 eicosyl group, the  $R^1$  group defining a three-dimensional volume, when rotated about an axis drawn through the  $SO_2$ -bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the  $SO_2$ -bonded 1-position and the center of 3,4-bond of a
- 15 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings. Alternatively, a  $R^1$  group is (ii) an  $-NR^7R^8$  group in which  $R^7$  and  $R^8$  are independently selected
- 20 from the group consisting of hydrido, hydrocarbyl, aryl, substituted aryl, arylhydrocarbyl, and substituted arylhydrocarbyl. More preferably, a  $R^1$  group is an  $-NR^7R^8$  group in which  $R^7$  and  $R^8$  are independently selected from the group consisting of a
- 25 hydrido, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl,  $R^a$ oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and a

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heterocyclo substituent, each of which substituent groups is optionally substituted with an -A-R-E-Y substituent;

- in such an -A-R-E-Y substituent, A is
- 5 selected from the group consisting of
- (1) -O-;
  - (2) -S-;
  - (3) -NR<sup>k</sup>-;
  - (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
  - 10 (5) -CO-O- or -O-CO-;
  - (6) -O-CO-O-;
  - (7) -HC=CH-;
  - (8) -NH-CO-NH-;
  - (9) -C≡C-;
  - 15 (10) -N=N-;
  - (11) -NH-NH-;
  - (12) -CS-N(R<sup>k</sup>) - or -N(R<sup>k</sup>)-CS-;
  - (13) -CH<sub>2</sub>-;
  - (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
  - 20 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
  - (16) -SO-; and
  - (17) -SO<sub>2</sub>-; or
  - (18) A is absent and R is directly bonded to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;
- 25 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,
- 30 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl,

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heteroaryl, cycloalkyl or heterocycloalkyl  
substituent is (i) unsubstituted or (ii) substituted  
with one or two radicals selected from the group  
consisting of a halo, alkyl, perfluoroalkyl,  
5 perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,  
alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylene-dioxy, hydroxycarbonylalkyl,  
hydroxycarbonylalkylamino, nitro, hydroxy,  
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl  
10 group;

the group E is selected from the group  
consisting of

- (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- 15 (3) -CO-;
- (4) -SO<sub>2</sub>(R<sup>g</sup>)- or -(R<sup>g</sup>)SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly  
20 to Y; and

the moiety Y is absent or is selected from  
the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
25 heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
30 aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group

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consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
5 (ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group;

or

$R^7$  and  $R^8$  taken together with the nitrogen atom  
to which they are bonded ( $-NR^7R^8$ ) form a group  
10 -G-A-R-E-Y wherein

G is a N-heterocyclo group;

the substituent A is selected from the group  
consisting of

- (1) -O-;
- 15 (2) -S-;
- (3)  $-NR^k-$ ;
- (4)  $-CO-N(R^k)$  or  $-N(R^k)-CO-$ ;
- (5)  $-CO-O-$  or  $-O-CO-$ ;
- (6)  $-O-CO-O-$ ;
- 20 (7)  $-HC=CH-$ ;
- (8)  $-NH-CO-NH-$ ;
- (9)  $-C\equiv C-$ ;
- (10)  $-N=N-$ ;
- (11)  $-NH-NH-$ ;
- 25 (12)  $-CS-N(R^k)-$  or  $-N(R^k)-CS-$ ;
- (13)  $-CH_2-$ ;
- (14)  $-O-CH_2-$  or  $-CH_2-O-$ ;
- (15)  $-S-CH_2-$  or  $-CH_2-S-$ ;
- (16)  $-SO-$ ; and
- 30 (17)  $-SO_2-$ ; or
- (18) A is absent and R is directly bonded  
to the N-heterocyclo group, G.

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The moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, 5 heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryl-oxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or 10 (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylene-dioxy, hydroxycarbonylalkyl, 15 hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group.

The moiety E is selected from the group consisting of

- 20 (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>(R<sup>g</sup>)- or -(R<sup>g</sup>)SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- 25 (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, 30 haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,

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perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxy carbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
5 aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
10 perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
(ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group;

$R^5$  and  $R^6$  are independently selected from  
15 the group consisting of a hydrido, alkyl, cycloalkyl,  
acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy,  
haloalkyl, haloalkyloxy, hydroxyalkyl, and a  
 $R^b R^c$  aminoalkyl substituent; or

$R^5$  and  $R^6$  together with the atoms to which  
20 they are bonded form a further aliphatic or aromatic  
carbocyclic or heterocyclic ring having 5- to 7-  
members.

In an above formula,  $R^a$  is selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
25 alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
arylalkylcarbonyl,  $R^b R^c$  aminoalkanoyl, haloalkanoyl,  
 $R^b R^c$  aminoalkyl, alkoxyalkyl, haloalkyl and an  
arylalkyloxy group;

$R^b$  and  $R^c$  are independently selected from the  
30 group consisting of a hydrido, alkanoyl, arylalkyl,  
aroyl, bisalkoxyalkyl, alkyl, haloalkyl,  
perfluoroalkyl, trifluoromethylalkyl,

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- perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl,  
heterocycloalkyl, heterocycloalkylcarbonyl, aryl,  
heterocyclo, heteroaryl, cycloalkylalkyl,  
aryloxyalkyl, heteroaryloxyalkyl,  
5 heteroarylalkoxyalkyl, heteroarylthioalkyl,  
arylsulfonyl, aralkanoyl, alkylsulfonyl,  
heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
alkyliminocarbonyl, aryliminocarbonyl,  
10 heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
alkoxycarbonyl, aryloxy carbonyl, aminoalkylcarbonyl,  
15 hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
amino group taken together with the amino nitrogen  
20 form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
two or three groups independently selected from  $R^f$   
25 substituents;
- $R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
arylalkylcarbonyl, alkoxycarbonyl or  
30 arylalkyloxycarbonyl group;



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$R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen (halo; F, Cl, Br, I), aryl, alkoxy, cyano, and  $R^d R^e$  amino;

$R^g$  is selected from the group consisting of a

5 hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy,

10 alkoxyaryl, alkoxyheteroaryl,  $R^h R^i$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl,

15 arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy,  $R^h R^i$ -aminocarbonyloxy,  $R^h R^i$ -aminocarbonyl,  $R^h R^i$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^h R^i$ -aminosulfonyl,  $R^h R^i$ -aminocarbonyl( $R^h$ )amino, trifluoromethylsulfonyl( $R^h$ )amino, heteroarylsulfonyl-

20 ( $R^h$ )amino, arylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )-aminocarbonyl, alkylsulfonyl( $R^h$ )amino, arylcarbonyl- ( $R^h$ )aminosulfonyl, and an alkylsulfonyl( $R^h$ )-aminocarbonyl substituent;

$R^h$  is selected from the group consisting of

25 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or

30 unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is optionally substituted by one or two groups.

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independently selected from R<sup>j</sup> substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

R<sup>i</sup> is selected from the group consisting of an  
5 arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or  
10 unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two R<sup>j</sup> substituents;

R<sup>j</sup> is selected from the group consisting of an  
15 arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a  
20 hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an  
25 alkyloxycarbonyl group; and

R<sup>k</sup> is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R<sup>C</sup>R<sup>d</sup>amino carbonyl, R<sup>C</sup>R<sup>d</sup>aminosulfonyl,  
30 R<sup>C</sup>R<sup>d</sup>aminoalkanoyl and R<sup>C</sup>R<sup>d</sup>aminoalkysulfonyl.

R<sup>20</sup> is (a) -O-R<sup>21</sup>, where R<sup>21</sup> is selected from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl,

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ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group and a pharmaceutically acceptable cation, (b) -NR<sup>13</sup>-O-R<sup>22</sup> wherein R<sup>22</sup> is a selectively removable protecting group such as a 2-tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ), C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, trisubstituted silyl group or o-nitrophenyl group, peptide synthesis resin and the like, wherein the trisubstituted silyl group is substituted with C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, or ar-C<sub>1</sub>-C<sub>6</sub>-alkyl or a mixture thereof, and R<sup>13</sup> is a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl or benzyl group, (c) -NR<sup>13</sup>-O-R<sup>14</sup>, where R<sup>13</sup> is as before and R<sup>14</sup> is hydrido, a pharmaceutically acceptable cation or C(V)R<sup>15</sup> where V is O (oxo) or S (thioxo) and R<sup>15</sup> is selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, aryloxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, heteroaryl and amino C<sub>1</sub>-C<sub>6</sub>-alkyl group wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, and C<sub>1</sub>-C<sub>6</sub>-alkanoyl radical, or (iii) wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) -NR<sup>23</sup>R<sup>24</sup>, where R<sup>23</sup> and R<sup>24</sup> are independently selected from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, amino C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, and an ar-C<sub>1</sub>-C<sub>6</sub>-

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alkyl group, or  $R^{23}$  and  $R^{24}$  together with the depicted nitrogen atom form a 5- to 8-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur.

5                   A compound of Formula C embraces a useful precursor compound, a pro-drug form of a hydroxamate and the hydroxamate itself, as well as amide compounds that can be used as intermediates and also as MMP inhibitor compounds. Thus, for example, where  
10  $R^{20}$  is  $-O-R^{21}$ , in which  $R^{21}$  is selected from the group consisting of a hydrido,  $C_1$ - $C_6$ -alkyl, aryl, ar- $C_1$ - $C_6$ -alkyl group and a pharmaceutically acceptable cation, a precursor carboxylic acid or ester is defined that can be readily transformed into a  
15 hydroxamic acid, as is illustrated in several Examples hereinafter. Such a carboxyl compound that is a precursor to a hydroxamate can also have activity as an inhibitor of MMP enzymes as is seen from the Inhibition Table of those Examples.

20                   Another useful precursor compound is defined when  $R^{20}$  is  $-NR^{13}-O-R^{22}$ , wherein  $R^{22}$  is a selectively removable protecting group and  $R^{13}$  is a hydrido or benzyl group, preferably a hydrido group. A selectively removable protecting group is  
25 exemplified as a 2-tetrahydropyranyl, benzyl, p-methoxybenzyloxycarbonyl (MOZ), benzyloxycarbonyl (BOC),  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_1$ - $C_6$ -alkoxy- $CH_2$ -,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_6$ -alkoxy- $CH_2$ -, trisubstituted silyl group, an o-nitrophenyl group, peptide synthesis  
30 resin and the like. A trisubstituted silyl group is

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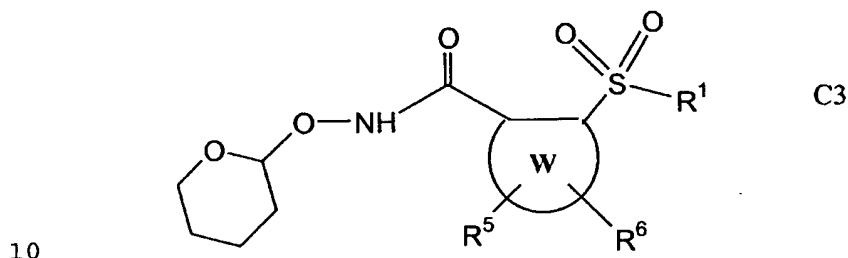
a silyl group substituted with C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, or ar-C<sub>1</sub>-C<sub>6</sub>-alkyl substituent groups or a mixture thereof such as a trimethylsilyl, triethylsilyl, dimethylisopropylsilyl, triphenylsilyl, t-butyl-  
5 butyldiphenylsilyl, diphenylmethylsilyl, a tribenzylsilyl group, and the like. Exemplary trisubstituted silyl protecting groups and their uses are discussed at several places in Greene et al., Protective Groups In Organic Synthesis, 2nd ed., John  
10 Wiley & Sons, Inc., New York (1991).

A contemplated peptide synthesis resin is solid phase support also known as a so-called Merrifield's Peptide Resin that is adapted for synthesis and selective release of hydroxamic acid  
15 derivatives as is commercially available from Sigma Chemical Co., St. Louis, MO. An exemplary peptide synthesis resin so adapted and its use in the synthesis of hydroxamic acid derivatives is discussed in Floyd et al., Tetrahedron Let., 37(44):8048-  
20 8048(1996).

A 2-tetrahydropyranyl (THP) protecting group is a particularly preferred selectively removable protecting group and is often used when R<sup>13</sup> is a hydrido group. A contemplated THP-protected  
25 hydroxamate compound of Formula A can be prepared by reacting the carboxylic acid precursor compound of Formula A [where R<sup>20</sup> is -O-R<sup>21</sup> and R<sup>21</sup> is a hydrido group] in water with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine in the presence of N-  
30 methylmorpholine, N-hydroxybenzotriazole hydrate and a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

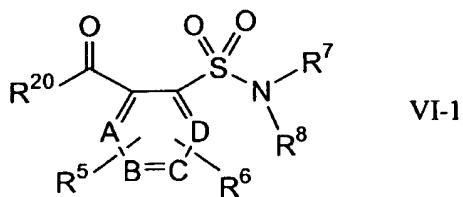
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hydrochloride. The resulting THP-protected hydroxamate corresponds in structure to Formula C3, below, where W, R<sup>1</sup>, R<sup>5</sup> and R<sup>6</sup> are as defined previously and more fully hereinafter. The THP protecting group is readily removable in an aqueous acid solution such as an aqueous mixture of p-toluenesulfonic acid or HCl and acetonitrile or methanol.



Another aspect of the invention contemplates a compound that corresponds in structure to Formula VI-1, below,

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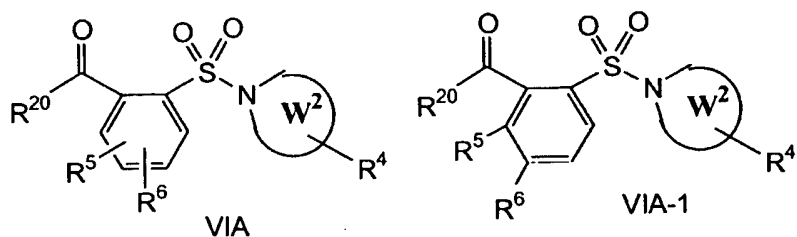
wherein each of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>20</sup> is as defined before, and in greater detail hereinafter, and each of A, B, C and D is carbon, nitrogen, sulfur or oxygen and is present or absent so that the depicted ring has 5- or 6-members. A hydroxamate compound of Formula VI-1 is a selective inhibitor of MMP-2 over both of MMP-1 and MMP-13. That is, a hydroxamate compound of Formula VI exhibits greater

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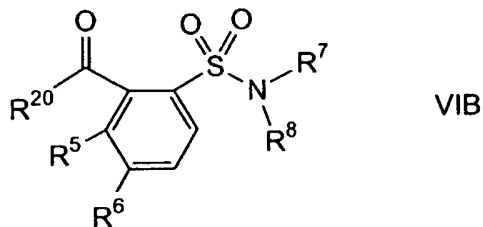
activity in inhibiting MMP-2 than in inhibiting either MMP-1 and usually also MMP-13.

A particularly preferred embodiment of this aspect of the invention is a compound that  
 5 corresponds in structure to Formulas VIA or VIA-1



wherein R<sup>20</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>4</sup> are as defined  
 10 before, ring structure W<sup>2</sup> including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 6-members, and R<sup>4</sup> is bonded at the 4-position relative to that depicted nitrogen atom when W<sup>2</sup> is a 6-membered ring and at the 3- or 4-position relative  
 15 to that depicted nitrogen when W<sup>2</sup> is a 5-membered ring. The ring structure W<sup>2</sup> is preferably a N-piperidinyl group that is itself preferably substituted as is discussed hereinafter.

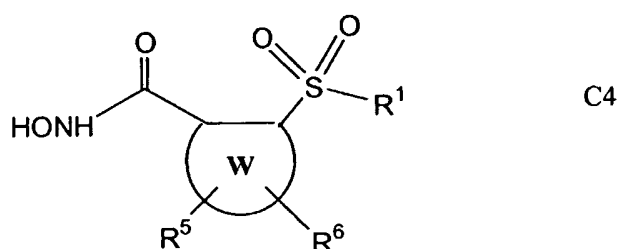
Another particularly preferred embodiment  
 20 of this aspect is a compound that corresponds in structure to Formula VIB



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wherein R<sup>20</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are as defined before.

A further embodiment of the present invention is directed to a sulfonyl aryl or  
 5 heteroaryl hydroxamic acid compound that can act as a matrix metalloprotease enzyme inhibitor. That compound corresponds in structure to Formula C4



10 wherein

the ring structure W is a 5- or 6-membered aromatic or heteroaromatic ring;

R<sup>1</sup> is a substituent containing a 5- or 6-  
 15 membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO<sub>2</sub>-group and having a length greater than about that of a hexyl group and less than about that of an eicosyl group, said R<sup>1</sup> defining a three-dimensional  
 20 volume, when rotated about an axis drawn through the SO<sub>2</sub>-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO<sub>2</sub>-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction  
 25 transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings;  
 and



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R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a

5 R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocyclooxy and a R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

or R<sup>5</sup> and R<sup>6</sup> together with the atoms to  
10 which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members.

Again, in some preferred embodiments, (ii), R<sup>1</sup> is an -NR<sup>7</sup>R<sup>8</sup> group in which R<sup>7</sup> and R<sup>8</sup> are  
15 independently selected from the group consisting of hydrido, hydrocarbyl, aryl, substituted aryl, arylhydrocarbyl, and substituted arylhydrocarbyl. More preferably still, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of a hydrido,  
20 alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, R<sup>a</sup>oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and a heterocyclo substituent, each of which substituent groups is optionally substituted with an -A-R-E-Y  
25 substituent;

in such an -A-R-E-Y substituent, A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- 30 (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;

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- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- 5 (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- 10 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;
- 15 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,
- 20 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted
- 25 with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylene-dioxy, hydroxycarbonylalkyl,
- 30 hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

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the group E is selected from the group consisting of

- (1)  $-\text{COR}^{\text{G}}-$  or  $-\text{R}^{\text{G}}\text{CO}-$ ;
- (2)  $-\text{CON}(\text{R}^{\text{K}})-$  or  $-(\text{R}^{\text{K}})\text{NCO}-$ ;
- 5 (3)  $-\text{CO}-$ ;
- (4)  $-\text{SO}_2(\text{R}^{\text{G}})-$  or  $-(\text{R}^{\text{G}})\text{SO}_2-$ ;
- (5)  $-\text{SO}_2-$ ;
- (6)  $-\text{N}(\text{R}^{\text{K}})-\text{SO}_2-$  or  $-\text{SO}_2-\text{N}(\text{R}^{\text{K}})-$ ; or
- (7) E is absent and R is bonded directly
- 10 to Y; and

- the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy,
- 15 heteroaryloxy, heteroaralkyl,  $\text{R}^{\text{a}}\text{oxyalkyl}$ , perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl,
  - 20 aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy,
  - 25 perfluoroalkyl, perfluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

More preferably yet,  $\text{R}^7$  and  $\text{R}^8$  taken together with the nitrogen atom to which they are bonded ( $-\text{NR}^7\text{R}^8$ ) form a group  $-\text{G}-\text{A}-\text{R}-\text{E}-\text{Y}$  wherein

G is a N-heterocyclo group;

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the substituent A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- 5 (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- 10 (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- 15 (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- 20 (18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, 25 heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) 30 unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a

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halo, alkyl, perfluoroalkyl, perfluoroalkoxy,  
perfluoroalkylthio, trifluoromethylalkyl, amino,  
alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylene-dioxy,  
hydroxycarbonylalkyl, hydroxycarbonylalkylamino,  
5 nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a  
alkoxycarbonyl group;

the moiety E is selected from the group  
consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- 10 (2) -CONR<sup>k</sup>- or -R<sup>k</sup>NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>(R<sup>G</sup>)- or -(R<sup>G</sup>)SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- 15 (7) E is absent and R is bonded directly  
to Y; and

the moiety Y is absent or is selected from  
the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
20 hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
25 aminoalkyl group, wherein the aryl, heteroaryl,  
aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
30 haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or

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(ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

The superscripted "R" groups, R<sup>a</sup>, R<sup>b</sup> and the like above and hereinafter are as defined before.

5           In one preferred embodiment, R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, hydrocarbyl, preferably C<sub>1</sub>-C<sub>4</sub> hydrocarbyl, hydroxylhydrocarbyl, hydroxyl, amino, R<sup>b</sup>R<sup>c</sup>aminohydrocarbyl, halo, nitro, cyano, hydrocarbyloxy, halohydrocarbyl, halohydrocarbyloxy, 10 hydroxyhydrocarbyl, dihydrocarbylamino, heterocyclo, heterocyclohydrocarbyl, heterocyclooxy, and a heterocyclothio group. More preferably, R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, 15 nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, and a R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent.

Contemplated aromatic or heteroaromatic rings include 1,2-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 4,5-pyridinylene, 2,3-pyrazinylene, 4,5-pyrimidinylene, and 5,6-pyrimidinylene groups. 1,2-Phenylene ( a 1,2-disubstituted phenyl ring) is a particularly preferred aromatic or heteroaromatic 20 ring, and is used illustratively herein as W.

As noted above, an R<sup>1</sup> substituent contains a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO<sub>2</sub>-group. An R<sup>1</sup> substituent also has 30 length, width and substitution requirements that are discussed in detail below. It is noted here, however, that a single- ringed or fused ring

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cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is not itself long enough to fulfill the length requirement for a preferred compound, particularly where  $R^1$  is  $NR^7R^8$ . As such, that  
5 cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical should itself be substituted.

Exemplary 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radicals that can constitute a portion of a  $R^1$   
10 substituent and are themselves substituted as discussed herein include phenyl, 2-, 3-, or 4-pyridyl, 2-naphthyl, 2-pyrazinyl, 2- or 5-pyrimidinyl, 2- or 3-benzo(b)thienyl, 8-purinyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-imidazolyl,  
15 cyclopentyl, cyclohexyl, 2- or 3-piperidinyl, 2- or 3-morpholinyl, 2- or 3-tetrahydropyranyl, 2-imidazolidinyl, 2- or 3-pyrazolidinyl and the like. A phenyl radical is particularly preferred and is used illustratively herein.

20 When examined along its longest chain of atoms, an  $R^1$  substituent (including  $NR^7R^8$  as an  $R^1$  substituent), including its own substituent when present, has a total length equivalent to a length that is greater than that of a fully extended  
25 saturated chain of six carbon atoms (a hexyl group); i.e., a length of a heptyl chain in staggered conformation or longer, and a length that is less than that of a fully extended saturated chain of about 20 carbons (an eicosyl group). Preferably,  
30 that length is about 8 to about 18 carbon atoms, even though many more atoms may be present in ring structures or substituents. This length requirement is discussed further below.

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Looked at more generally, and aside from specific moieties from which it is constructed, an  $R^1$  substituent (radical, group or moiety) has a length of a heptyl group or greater. Such an  $R^1$  substituent also has a length that is less than that of an eicosyl group. That is to say that a  $R^1$  is a substituent having a length greater than that of a fully extended saturated six carbon chain and shorter than that of a fully extended saturated twenty carbon chain, and more preferably, a length greater than that of a octyl group and less than that of a palmityl group. The radical chain lengths are measured along the longest linear atom chain in the radical, following the skeletal atoms of a ring where necessary. Each atom in the chain, e.g. carbon, oxygen or nitrogen, is presumed to be carbon for ease in calculation.

Such lengths can be readily determined by using published bond angles, bond lengths and atomic radii, as needed, to draw and measure a chain, or by building models using commercially available kits whose bond angles, lengths and atomic radii are in accord with accepted, published values. Radical (substituent) lengths can also be determined somewhat less exactly by presuming, as is done here, that all atoms have bond lengths of saturated carbon, that unsaturated and aromatic bonds have the same lengths as saturated bonds and that bond angles for unsaturated bonds are the same as those for saturated bonds, although the above-mentioned modes of measurement are preferred. For example, a 4-phenyl or 4-pyridyl group has a length of a four carbon chain, as does a propoxy group, whereas a biphenyl



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group has a length of about an eight carbon chain using a contemplated measurement mode.

In addition, an  $R^1$  substituent, when rotated about an axis drawn through the  $SO_2$ -bonded 1-position and the 4-position of a 6-membered ring radical or the  $SO_2$ -bonded 1-position and through the 3,4 bond of a 5-membered ring radical defines a three-dimensional volume whose widest dimension has the width of about one furanyl ring to about the width of two phenyl rings in a direction transverse to that axis to rotation.

When utilizing this width or volume criterion, a fused ring system such as a naphthyl or purinyl radical is considered to be a 6- or 5-membered ring that is substituted at appropriate positions numbered from the  $SO_2$ -linkage that is deemed to be at the 1-position as discussed before. Thus, a 2-naphthyl substituent or an 8-purinyl substituent is an appropriately sized  $R^1$  radical as to width when examined using the above rotational width criterion. On the other hand, a 1-naphthyl group or a 7- or 9-purinyl group is too large upon rotation and is excluded.

As a consequence of these length and width requirements,  $R^1$  substituents such as 4-(phenyl)phenyl [biphenyl], 4-(4'-methoxyphenyl)-phenyl, 4-(phenoxy)phenyl, 4-(thiophenyl)phenyl [4-(phenylthio)phenyl], 4-(phenylazo)phenyl 4-(phenylureido)phenyl, 4-(anilino)phenyl, 4-(nicotinamido)phenyl, 4-(isonicotinamido)phenyl, 4-(picolinamido)phenyl and 4-(benzamido)phenyl are among particularly preferred  $R^1$  substituents, with

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4-(phenoxy)phenyl and 4-(thiophenyl)phenyl being most preferred.

An SO<sub>2</sub>-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is a 5- or 6-membered single-ring that is itself substituted with one other substituent, R<sup>4</sup>. The SO<sub>2</sub>-linked single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is R<sup>4</sup>-substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring. The cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical to which R<sup>4</sup> is bonded in some embodiments is preferably a phenyl group, so that R<sup>1</sup> is preferably PhR<sup>4</sup> in which R<sup>4</sup> is bonded at the 4-position of the SO<sub>2</sub>-linked phenyl (Ph) radical, and in which R<sup>4</sup> can itself be optionally substituted as is discussed hereinafter. In other embodiments, a heterocyclo or heteroaryl radical is preferred over a phenyl radical, with the R<sup>4</sup> substituent being linked at the 4-position relative to the bond between the ring and the SO<sub>2</sub> group.

A contemplated R<sup>4</sup> substituent can be a single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl group or another substituent having a chain length of 3 to about 14 carbon atoms such as a hydrocarbyl or hydrocarbyloxy group [e.g., C<sub>3</sub>-C<sub>14</sub> hydrocarbyl or O-C<sub>2</sub>-C<sub>14</sub> hydrocarbyl], a phenyl group, a phenoxy group [-OC<sub>6</sub>H<sub>5</sub>], a thiophenoxy group [phenylsulfanyl; -SC<sub>6</sub>H<sub>5</sub>], an anilino group [-NHC<sub>6</sub>H<sub>5</sub>], a phenylazo group [-N<sub>2</sub>C<sub>6</sub>H<sub>5</sub>], a phenylureido group [aniline carbonylamino; -NHC(O)NH-C<sub>6</sub>H<sub>5</sub>], a benzamido

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group  $[-\text{NHC}(\text{O})\text{C}_6\text{H}_5]$ , a nicotinamido group  
[3- $\text{NHC}(\text{O})\text{C}_5\text{H}_4\text{N}$ ], an isonicotinamido group  
[4- $\text{NHC}(\text{O})\text{C}_5\text{H}_4\text{N}$ ], or a picolinamido group  
[2- $\text{NHC}(\text{O})\text{C}_5\text{H}_4\text{N}$ ]. Additionally contemplated  $\text{R}^4$   
5 substituent groups include a heterocyclo,  
heterocyclohydrocarbyl, arylhydrocarbyl,  
arylheterocyclohydrocarbyl, heteroarylhydrocarbyl,  
heteroarylheterocyclo-hydrocarbyl,  
arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl,  
10 hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl,  
arylcarbonylhydrocarbyl, arylazoaryl,  
arylhydrazinoaryl, hydrocarbyl-thiohydrocarbyl,  
hydrocarbylthioaryl, arylthiohydrocarbyl,  
heteroarylthiohydrocarbyl,  
15 hydrocarbylthioarylhydrocarbyl, arylhydrocarbyl-  
thiohydrocarbyl, arylhydrocarbylthioaryl,  
arylhydrocarbylamino, heteroarylhydrocarbylamino, or  
a heteroarylthio group.

A contemplated  $\text{R}^4$  substituent can itself  
20 also be substituted with one or more substituent  
radicals at the meta- or para-position or both of a  
six-membered ring with a single atom or a substituent  
containing a longest chain of up to ten atoms,  
excluding hydrogen. Exemplary substituent radicals  
25 include a halo, hydrocarbyl, hydrocarbyloxy, nitro,  
cyano, perfluorohydrocarbyl, trifluoromethyl-  
hydrocarbyl, hydroxy, mercapto, hydroxycarbonyl,  
aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl,  
heteroaryloxy, heteroarylthio, heteroarylamino,  
30 heteroarhydrocarbyl, hydrocarbyloxycarbonyl-  
hydrocarbyl, heterocycloxy, hydroxycarbonyl-  
hydrocarbyl, heterocyclothio, heterocycloamino,

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- cyclohydrocarbyloxy, cyclohydrocarbylthio,  
cyclohydrocarbylamino, heteroarylhydrocarbyloxy,  
heteroarylhydrocarbylthio, heteroaryl-  
hydrocarbylamino, arylhydrocarbyloxy,  
5 arylhydrocarbylthio, arylhydrocarbylamino,  
heterocyclic, heteroaryl, hydroxycarbonyl-  
hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl,  
arylcarbonyl, arylhydrocarbyloyl, hydrocarboyloxy,  
arylhydrocarboyloxy, hydroxyhydrocarbyl, hydroxy-  
10 hydrocarbyloxy, hydrocarbylthio, hydrocarbyloxy-  
hydrocarbylthio, hydrocarbyloxycarbonyl,  
hydroxycarbonylhydrocarbyloxy, hydrocarbyloxy-  
carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-  
hydrocarbylthio, hydrocarbyloxycarbonyl-  
15 hydrocarbyloxy, hydrocarbyloxycarbonyl-  
hydrocarbylthio, amino, hydrocarbylcarbonylamino,  
arylcarbonylamino, cyclohydrocarbylcarbonylamino,  
heterocyclohydrocarbylcarbonylamino,  
arylhydrocarbylcarbonylamino, heteroaryl-  
20 carbonylamino, heteroarylhydrocarbylcarbonylamino,  
heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,  
arylsulfonylamino, arylhydrocarbylsulfonylamino,  
heteroarylsulfonylamino, heteroarylhydrocarbyl-  
sulfonylamino, cyclohydrocarbylsulfonylamino,  
25 heterocyclohydrocarbylsulfonylamino and N-  
monosubstituted or N,N-disubstituted aminohydrocarbyl  
group wherein the substituent(s) on the nitrogen are  
selected from the group consisting of hydrocarbyl,  
aryl, arylhydrocarbyl, cyclohydrocarbyl,  
30 arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,  
and hydrocarboyloxy, or wherein the nitrogen and two  
substituents attached thereto form a 5- to 8-membered  
heterocyclic or heteroaryl ring group.

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Thus, initial studies indicate that so long as the length, substitution and width (volume upon rotation) requirements of an SO<sub>2</sub>-linked R<sup>1</sup> substituent discussed herein are met, an R<sup>1</sup> substituent can be extremely varied.

A particularly preferred R<sup>4</sup> substituent of an SO<sub>2</sub>-linked Ph group is a single-ringed aryl or heteroaryl, phenoxy, thiophenoxy, phenylazo, phenylureido, nicotinamido, isonicotinamido, picolinamido, anilino or benzamido group that is unsubstituted or is itself substituted (optionally substituted) at the para-position when a 6-membered ring or the 3- or 4-position when a 5-membered ring. Here, single atoms such as halogen moieties or substituents that contain one to a chain of about ten atoms other than hydrogen such as C<sub>1</sub>-C<sub>10</sub> hydrocarbyl, C<sub>1</sub>-C<sub>9</sub> hydrocarbyloxy or carboxyethyl groups can be used.

Exemplary particularly preferred PhR<sup>4</sup> (particularly preferred R<sup>1</sup>) substituents include biphenyl, 4-phenoxyphenyl, 4-thiophenoxyphenyl, 4-benzamidophenyl, 4-phenylureido, 4-anilinophenyl, 4-nicotinamido, 4-isonicotinamido, and 4-picolinamido. Exemplary particularly preferred R<sup>4</sup> groups contain a 6-membered aromatic ring and include a phenyl group, a phenoxy group, a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group and a benzamido group.

More specifically, a particularly preferred sulfonyl butanhydroxamate compounds has an R<sup>4</sup> substituent that is a phenyl group, a phenoxy group,

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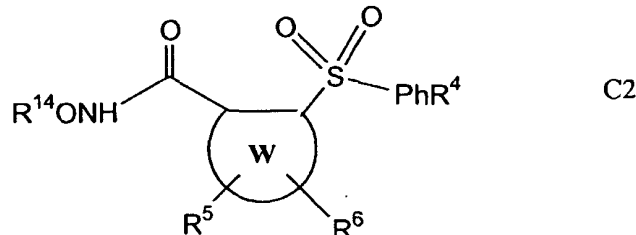
a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group or a benzamido group that is itself optionally substituted at its own meta or para-position or both with a moiety that is selected from the group consisting of a halogen, a halohydrocarbyl group, a halo C<sub>1</sub>-C<sub>9</sub> hydrocarbyloxy group, a perfluoro C<sub>1</sub>-C<sub>9</sub> hydrocarbyl group, a C<sub>1</sub>-C<sub>9</sub> hydrocarbyloxy (-O-C<sub>1</sub>-C<sub>9</sub> hydrocarbyl) group, a C<sub>1</sub>-C<sub>10</sub> hydrocarbyl group, a di-C<sub>1</sub>-C<sub>9</sub> hydrocarbylamino [-N(C<sub>1</sub>-C<sub>9</sub> hydrocarbyl)(C<sub>1</sub>-C<sub>9</sub> hydrocarbyl)] group, a carboxyl C<sub>1</sub>-C<sub>8</sub> hydrocarbyl (C<sub>1</sub>-C<sub>8</sub> hydrocarbyl-CO<sub>2</sub>H) group, a C<sub>1</sub>-C<sub>4</sub> hydrocarbyloxy carbonyl C<sub>1</sub>-C<sub>4</sub> hydrocarbyl [C<sub>1</sub>-C<sub>4</sub> hydrocarbyl-O-(CO)-C<sub>1</sub>-C<sub>4</sub> hydrocarbyl] group, a C<sub>1</sub>-C<sub>4</sub> hydrocarbyloxycarbonyl C<sub>1</sub>-C<sub>4</sub> hydrocarbyl [C<sub>1</sub>-C<sub>4</sub> hydrocarbyl(CO)-O-C<sub>1</sub>-C<sub>4</sub> hydrocarbyl] group and a C<sub>1</sub>-C<sub>8</sub> hydrocarbyl carboxamido [-NH(CO)-C<sub>1</sub>-C<sub>8</sub> hydrocarbyl] group, or is substituted at the meta- and para-positions by two methyl groups or by a C<sub>1</sub>-C<sub>2</sub> alkylenedioxy group such as a methylenedioxy group.

Inasmuch as a contemplated SO<sub>2</sub>-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is itself preferably substituted with a 6-membered aromatic ring, two nomenclature systems are used together herein for ease in understanding substituent positions. The first system uses position numbers for the ring directly bonded to the SO<sub>2</sub>-group, whereas the second system uses ortho, meta or para for the position of one or more substituents of a 6-membered ring bonded to a SO<sub>2</sub>-linked

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cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical. When a  $R^4$  substituent is other than a 6-membered ring, substituent positions are numbered from the position of linkage to the aromatic or heteroaromatic ring. Formal chemical nomenclature is used in naming particular compounds.

Thus, the 1-position of an above-discussed  $SO_2$ -linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is the position at which the  $SO_2$ -group is bonded to the ring. The 4- and 3-positions of rings discussed here are numbered from the sites of substituent bonding from the  $SO_2$ -linkage as compared to formalized ring numbering positions used in heteroaryl nomenclature.



In some preferred embodiments, a contemplated compound corresponds in structure to Formula C2, wherein W,  $R^5$ ,  $R^6$  and  $R^{14}$  are as defined above, Ph is phenyl substituted at the 4-position with substituent  $R^4$  that is defined hereinabove.

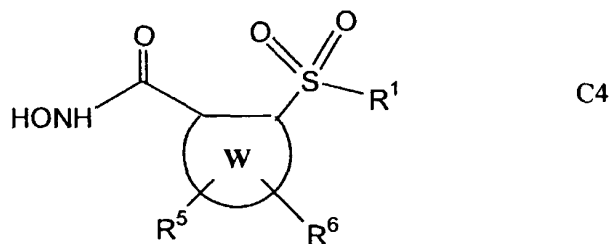
The length of a  $R^1$  substituent bonded to the  $SO_2$  group is believed to play a role in the overall activity of a contemplated inhibitor compound against MMP enzymes generally. Thus, a compound having an  $R^1$  substituent that is shorter in length

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than a heptyl group, e.g., a 4-methoxyphenyl group, typically exhibits moderate to poor inhibitory activity against all of the MMP enzymes, whereas compounds whose R<sup>1</sup> substituents have a length of about an heptyl chain or longer, e.g., a 4-phenoxyphenyl group that has a length of about a nine-carbon chain, typically exhibit good to excellent potencies against MMP-13 or MMP-2 and also selectivity against MMP-1. Exemplary data are provided in the Inhibition Tables hereinafter in which the activities of the above two compounds can be compared.

In view of the above-discussed preferences, compounds corresponding in structure to particular formulas constitute particularly preferred embodiments.

In one of those embodiments, a contemplated compound corresponds in structure to Formula C4, below,



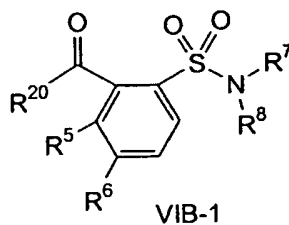
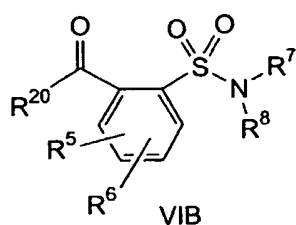
wherein W, R<sup>1</sup>, R<sup>5</sup>, and R<sup>6</sup> are as defined above, and R<sup>1</sup> is preferably PhR<sup>4</sup>, as is also defined above.

25 Again taking into account the before-stated preference that W be a 1,2-phenylene radical and the preference for R<sup>1</sup> being PhR<sup>4</sup>, particularly preferred compounds correspond in structure to Formulas VIB,

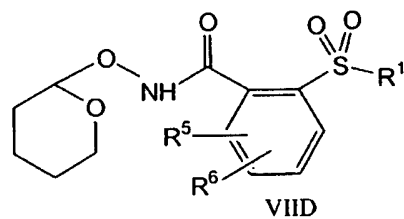
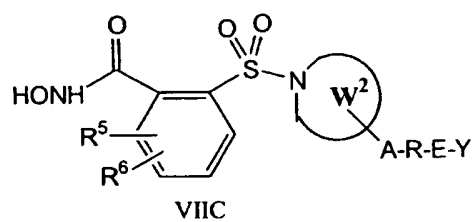
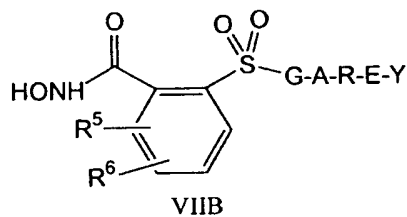
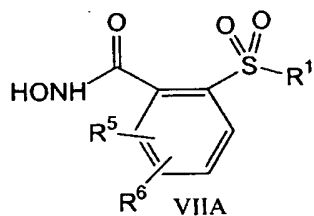
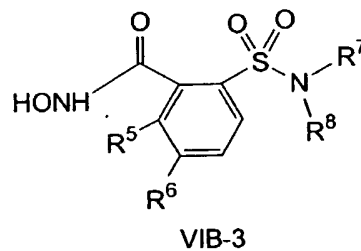
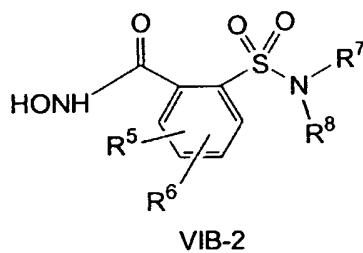


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VIB-1, VIB-2, VIB-3, VII, VII-B, VIIC, VIID, VIIE, VIII and, VIIIB, below, wherein the above definitions for -A-R-E-Y, -G-A-R-E-Y,  $W^2$ ,  $R^1$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^{20}$  also apply, and wherein the substituent -A-R-E-Y is bonded to ring structure  $W^2$  or a depicted ring structure.

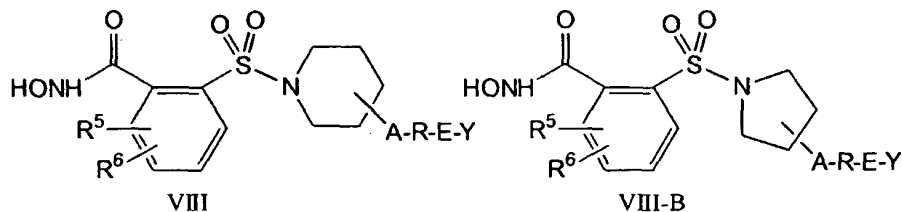
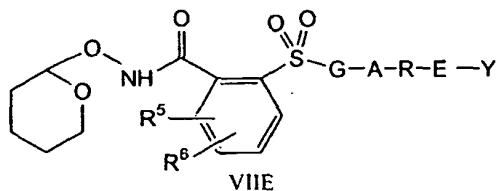


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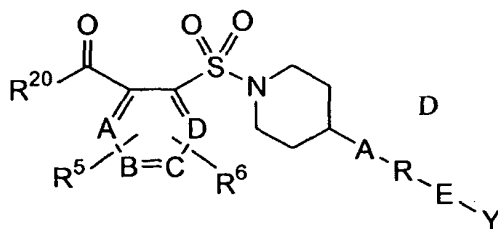
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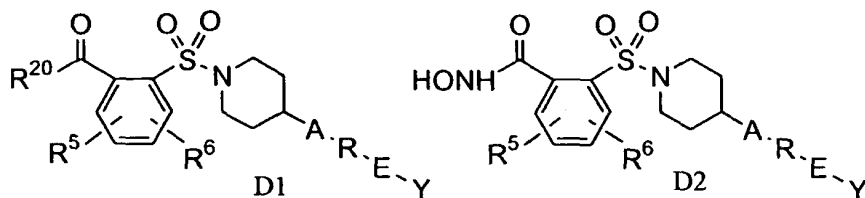


5                      The compounds that correspond in structure to Formulas D, D1, D2, D3 and D4, below, wherein the above definitions for -A-R-E-Y, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, and R<sup>20</sup> also apply and wherein each of A, B, C and D of the ring structure is carbon, nitrogen, sulfur or oxygen

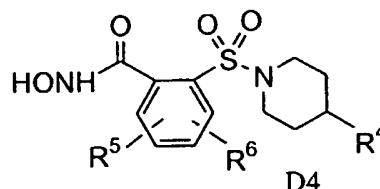
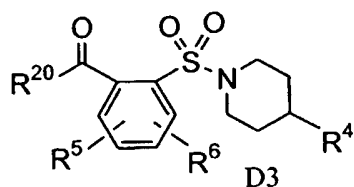
10 that is present or absent so that the depicted ring has 5- or 6-members, are also among the particularly preferred compounds contemplated herein and can be viewed as subsets of compounds of Formula VIB.



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The compound of Example 24 has a structure that corresponds to that of Formula D2. In that

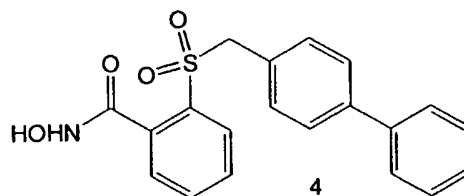
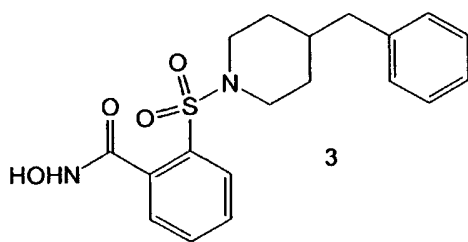
5 compound,  $R^5$  and  $R^6$  are both methoxy, the A moiety is a sulfur atom, -S-, R is 1,4-phenylene; E is absent and the moiety Y is hydrido. The compound of Example 25 also corresponds in structure to Formula D2.

There,  $R^5$  and  $R^6$  are again both methoxy, the A moiety

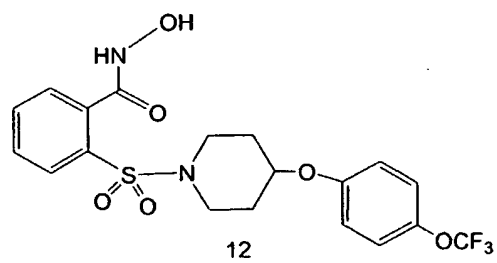
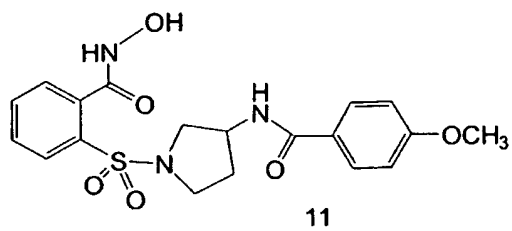
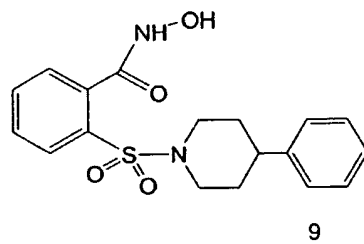
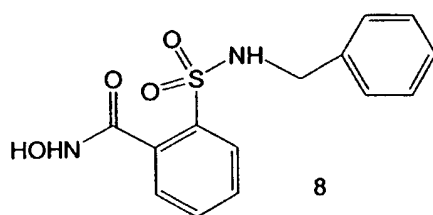
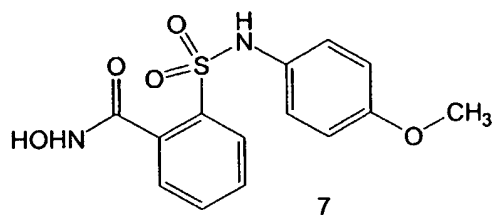
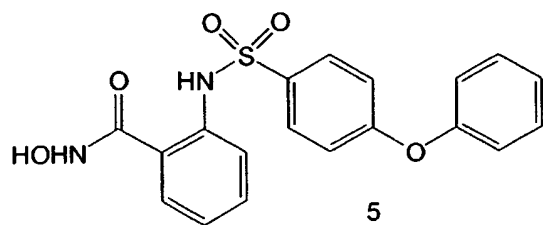
10 is an oxygen atom, -O-, R is 1,4-phenylene, E is absent and the moiety Y is a dialkoxy-substituted phenyl (aryl) group.

Particularly preferred compounds contemplated herein are illustrated hereinbelow,

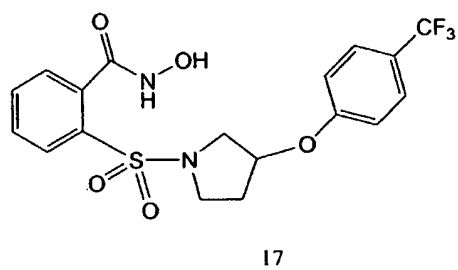
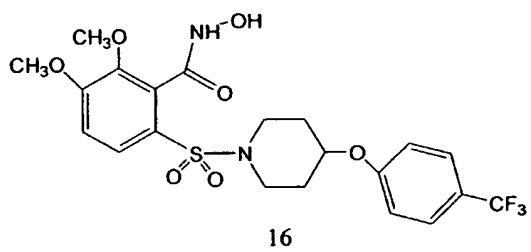
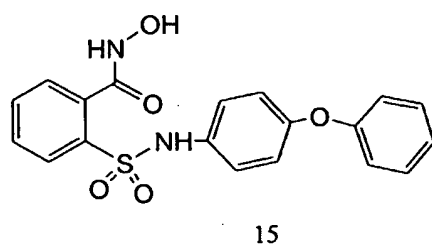
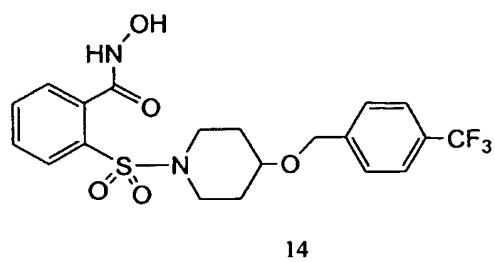
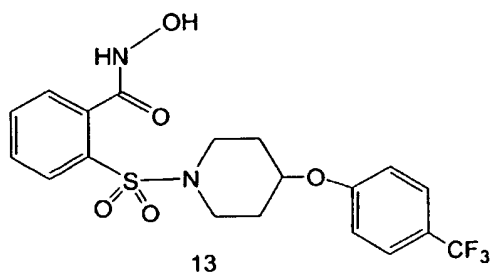
15 along with the number of the specific Example in which each is prepared.



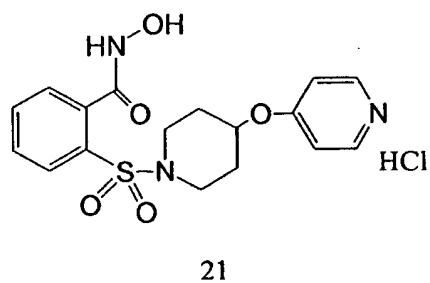
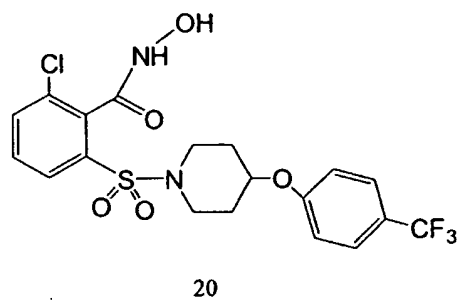
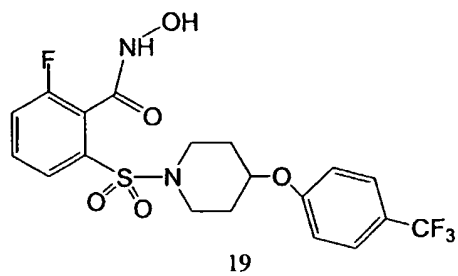
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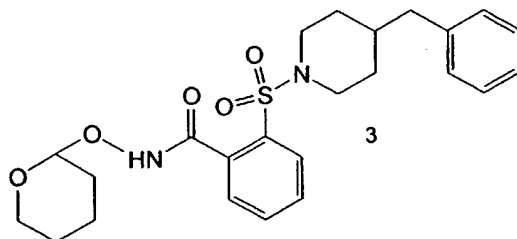
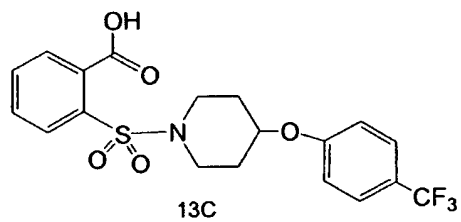
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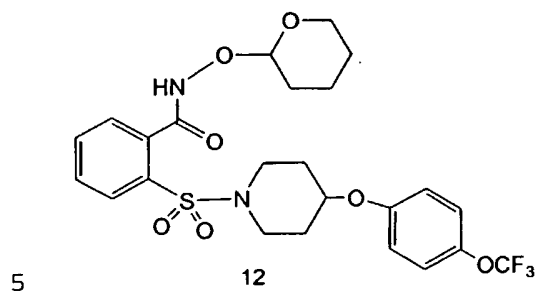
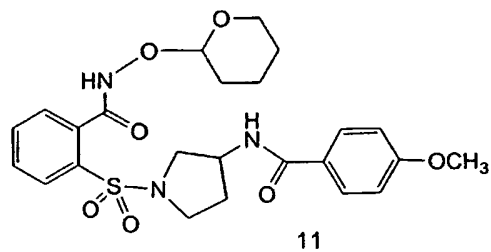
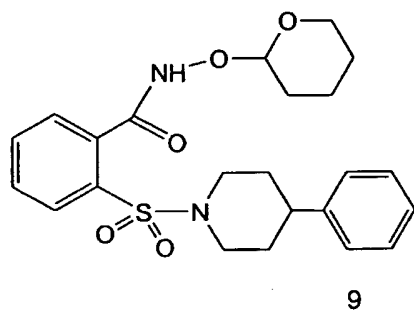
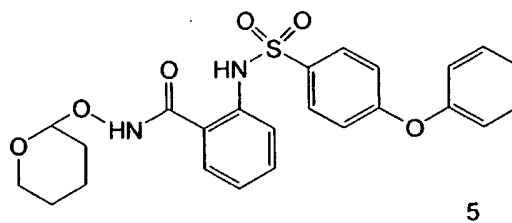
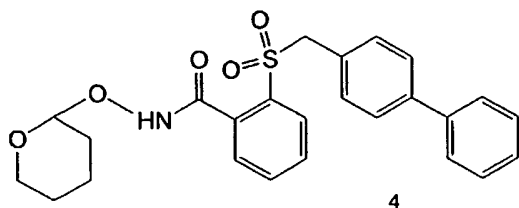
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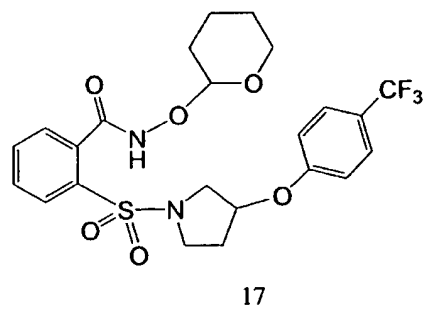
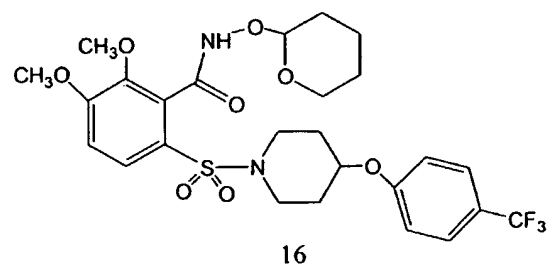
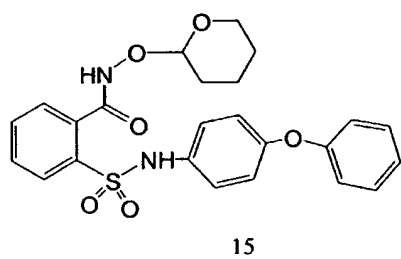
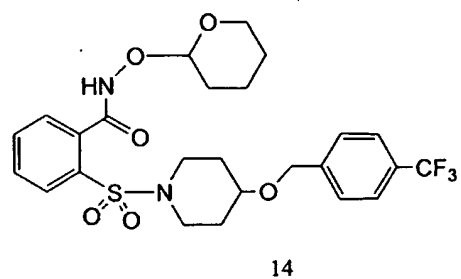
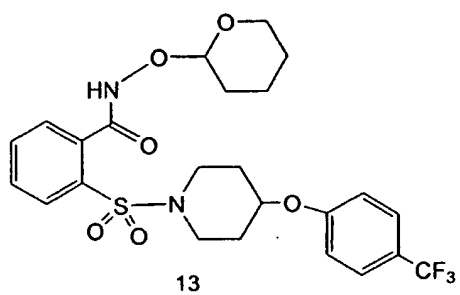


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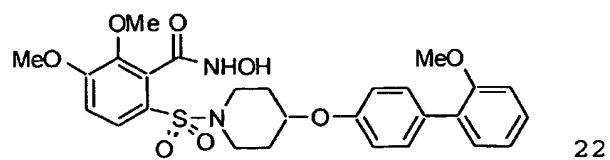
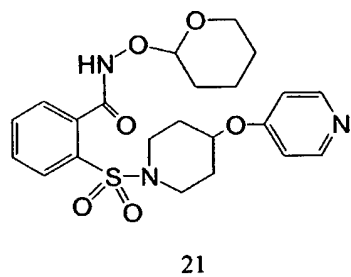
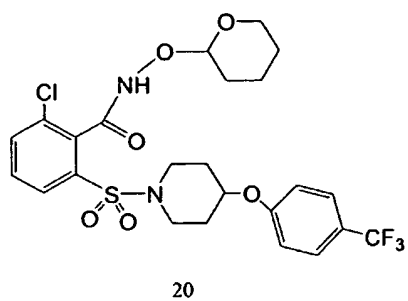
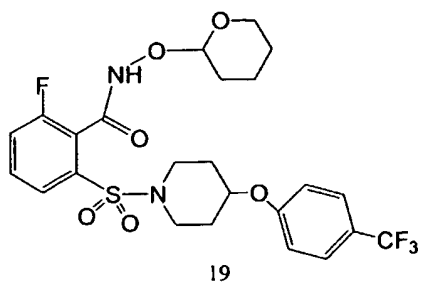
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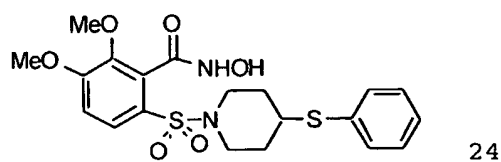
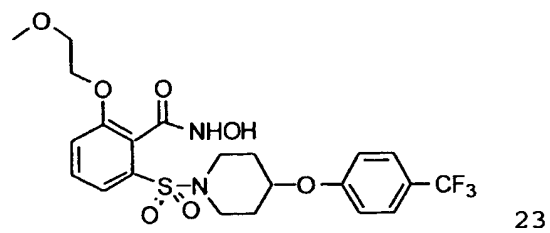




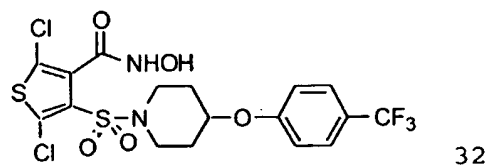
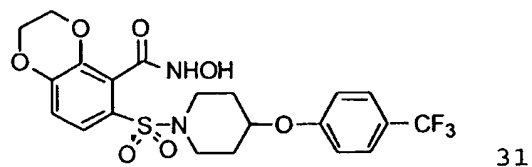
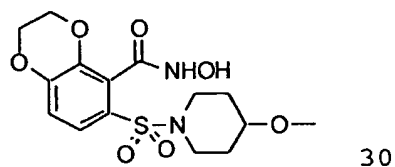
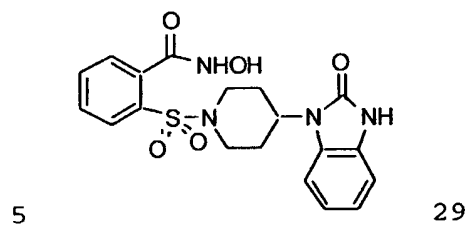
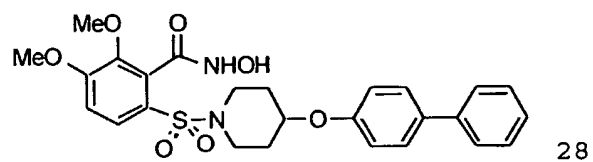
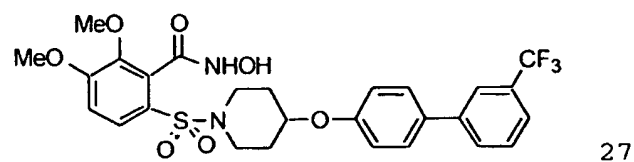
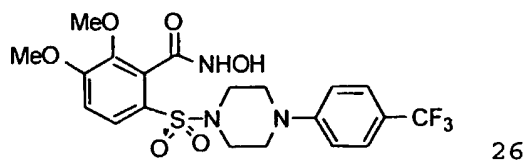
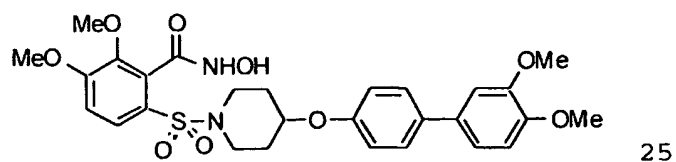
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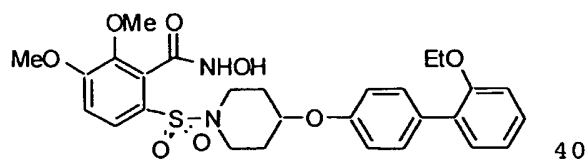
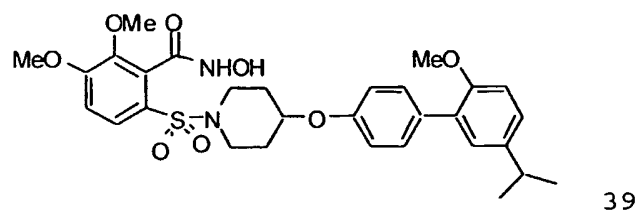
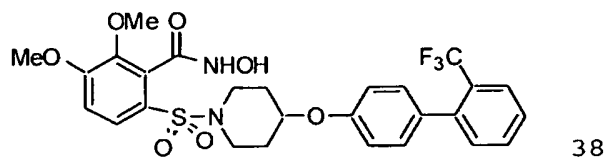
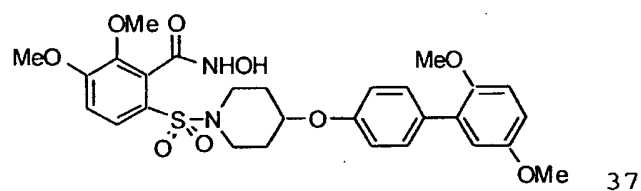
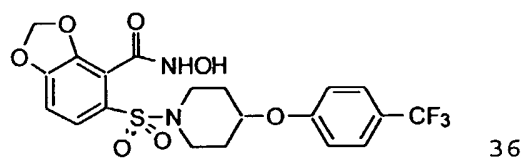
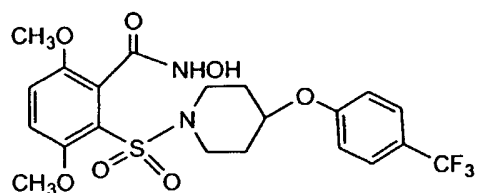
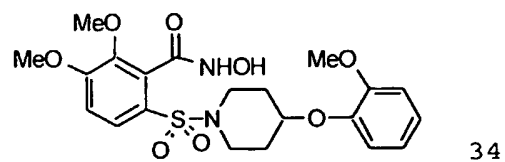
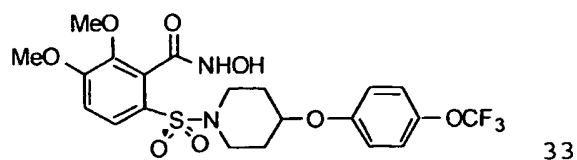
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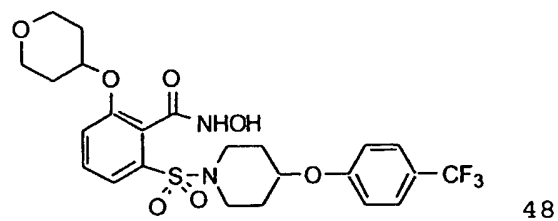
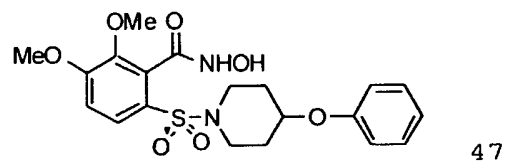
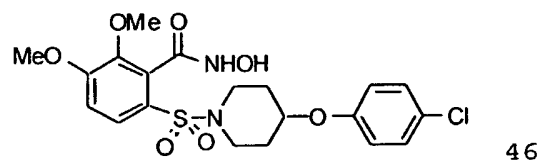
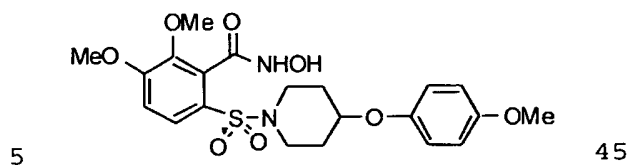
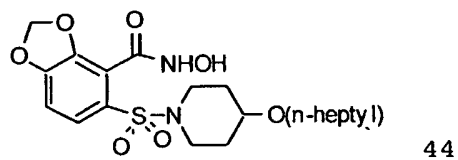
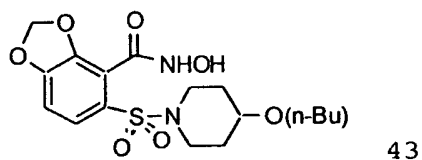
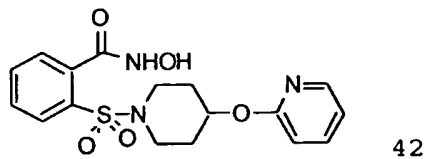
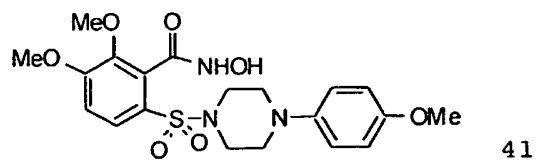
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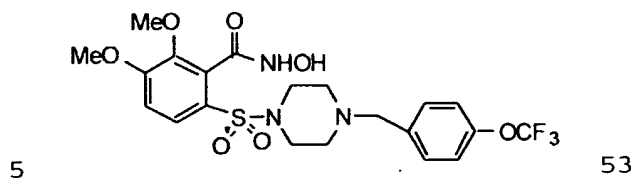
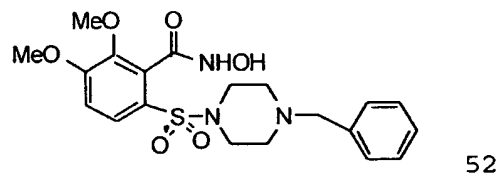
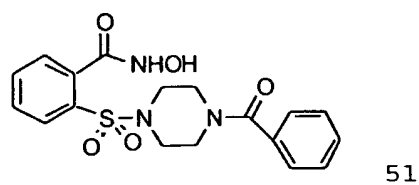
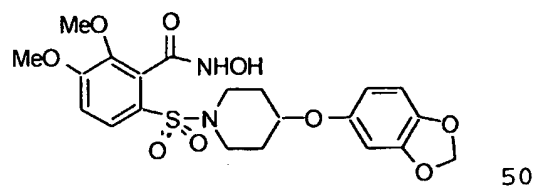
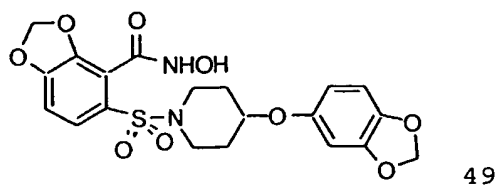
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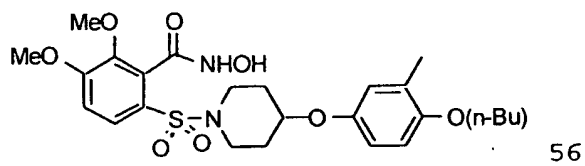
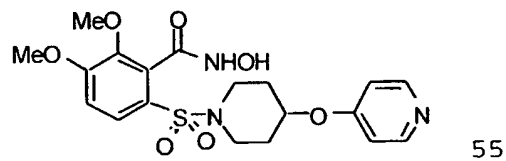
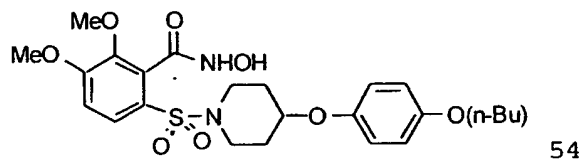
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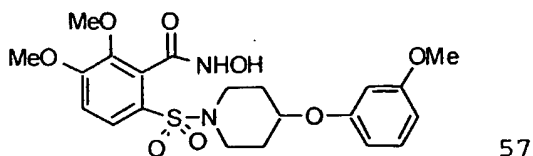
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The word "hydrocarbyl" is used herein as a short hand term to include straight and branched chain aliphatic as well as alicyclic groups or radicals that contain only carbon and hydrogen. Thus, alkyl, alkenyl and alkynyl groups are contemplated, whereas aromatic hydrocarbons such as phenyl and naphthyl groups, which strictly speaking are also hydrocarbyl groups, are referred to herein as aryl groups or radicals, as discussed hereinafter. Where a specific aliphatic hydrocarbyl substituent group is intended, that group is recited; i.e., C<sub>1</sub>-C<sub>4</sub> alkyl, methyl or dodecenyl. Exemplary hydrocarbyl groups contain a chain of 1 to about 12 carbon atoms, and preferably one to about 10 carbon atoms.

A particularly preferred hydrocarbyl group is an alkyl group. As a consequence, a generalized, but more preferred substituent can be recited by replacing the descriptor "hydrocarbyl" with "alkyl" in any of the substituent groups enumerated herein.

Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, decenyl and the like. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl,

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decynyl, 1-butyryl, 2-butyryl, 3-butyryl, and the like.

Usual chemical suffix nomenclature is followed when using the word "hydrocarbyl" except that the usual practice of removing the terminal "yl" and adding an appropriate suffix is not always followed because of the possible similarity of a resulting name to one or more substituents. Thus, a hydrocarbyl ether is referred to as a "hydrocarbyloxy" group rather than a "hydrocarboxy" group as may possibly be more proper when following the usual rules of chemical nomenclature. On the other hand, a hydrocarbyl group containing a -C(O)O- functionality is referred to as a hydrocarbonyl group inasmuch as there is no ambiguity in using that suffix. As a skilled worker will understand, a substituent that cannot exist such as a C<sub>1</sub> alkenyl group is not intended to be encompassed by the word "hydrocarbyl".

The term "carbonyl", alone or in combination, means a -C(=O)- group wherein the remaining two bonds (valences) are independently substituted. The term "thiol" or "sulfhydryl", alone or in combination, means a -SH group. The term "thio" or "thia", alone or in combination, means a thiaether group; i.e., an ether group wherein the ether oxygen is replaced by a sulfur atom, as in a thiophenoxy group (C<sub>6</sub>H<sub>5</sub>-S-).

The term "amino", alone or in combination, means an amine or -NH<sub>2</sub> group, whereas the term monosubstituted amino, alone or in combination, means a substituted amine -N(H)(substituent) group wherein one hydrogen atom is replaced with a substituent, and

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disubstituted amine means a  $-N(\text{substituent})_2$  wherein two hydrogen atoms of the amino group are replaced with independently selected substituent groups.

Amines, amino groups and amides are classes that can be designated as primary ( $I^\circ$ ), secondary ( $II^\circ$ ) or tertiary ( $III^\circ$ ) or unsubstituted, mono-substituted or di-substituted depending on the degree of substitution of the amino nitrogen. Quaternary amine ( $IV^\circ$ ) means a nitrogen with four substituents

10  $[-N^+(\text{substituent})_4]$  that is positively charged and accompanied by a counter ion or N-oxide means one substituent is oxygen and the group is represented as  $[-N^+(\text{substituent})_3-O^-]$ ; i.e., the charges are internally compensated.

15 The term "cyano", alone or in combination, means a  $-C\text{-triple bond-N}$  ( $-CN$ ) group. The term "azido", alone or in combination, means an  $-N\text{-double bond-N-double bond-N-}$  ( $-N=N=N-$ ).

The term "hydroxyl", alone or in combination, means a  $-OH$  group. The term "nitro", alone or in combination, means a  $-NO_2$  group.

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The term "azo", alone or in combination, means a  $-N=N-$  group wherein the bonds at the terminal positions are independently substituted. The term

25 "hydrazino", alone or in combination, means a  $-NH-NH-$  group wherein the remaining two bonds (valences) are independently substituted. The hydrogen atoms of the hydrazino group can be replaced, independently, with substituents and the nitrogen atoms can form acid

30 addition salts or be quaternized.

The term "sulfonyl", alone or in combination, means a  $-S(O)_2-$  group wherein the remaining two bonds (valences) can be independently



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substituted. The term "sulfoxido", alone or in combination, means a  $-S(=O)-$  group wherein the remaining two bonds (valences) can be independently substituted. The term "sulfonylamide", alone or in combination, means a  $-S(=O)_2-N=$  group wherein the remaining three bonds (valences) are independently substituted. The term "sulfinamido", alone or in combination, means a  $-S(=O)_1N=$  group wherein the remaining three bonds (valences) are independently substituted. The term "sulfenamide", alone or in combination, means a  $-S-N=$  group wherein the remaining three bonds (valences) are independently substituted.

The term "hydrocarbyloxy", alone or in combination, means an hydrocarbyl ether radical wherein the term hydrocarbyl is as defined above. Examples of suitable hydrocarbyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cyclohydrocarbyl", alone or in combination, means a hydrocarbyl radical that contains 3 to about 8 carbon atoms, preferably from about 3 to about 6 carbon atoms, and is cyclic. The term "cyclohydrocarbylhydrocarbyl" means an hydrocarbyl radical as defined above which is substituted by a cyclohydrocarbyl as also defined above. Examples of such cyclohydrocarbylhydrocarbyl radicals include cyclopropyl, cyclobutyl, cyclopentenyl, cyclohexyl cyclooctynyl and the like.

The term "aryl", alone or in combination, means a phenyl or naphthyl radical that optionally carries one or more substituents selected from hydrocarbyl, hydrocarbyloxy, halogen, hydroxy, amino,

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nitro and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, and the like. The term "arylhydrocarbyl", alone or in combination, means an hydrocarbyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "arylhydrocarbyloxycarbonyl", alone or in combination, means a radical of the formula -C(O)-O-arylhydrocarbyl in which the term "arylhydrocarbyl" has the significance given above. An example of an arylhydrocarbyloxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "aromatic ring" in combinations such as substituted-aromatic ring sulfonamide, substituted-aromatic ring sulfinamide or substituted-aromatic ring sulfenamide means aryl or heteroaryl as defined above.

The terms "hydrocarbyloyl" or "hydrocarbylcarbonyl", alone or in combination, mean an acyl radical derived from an hydrocarbylcarboxylic acid, examples of which include acetyl, propionyl, acryloyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cyclohydrocarbylcarbonyl" means an acyl group derived from a monocyclic or bridged cyclohydrocarbylcarboxylic acid such as cyclopropanecarbonyl, cyclohexenecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cyclohydrocarbylcarboxylic acid that is optionally substituted by, for example, a hydrocarbyloylamino group, such as 1,2,3,4-

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tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The terms "arylhydrocarbyloyl" or "arylhydrocarbylcarbonyl" mean an acyl radical derived from an aryl-substituted hydrocarbylcarboxylic acid such as phenylacetyl, 3-phenylpropenyl (cinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminocinnamoyl, 4-methoxycinnamoyl and the like.

The terms "aroyl" or "arylcarbonyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The heterocyclyl (heterocyclo) or heterocyclohydrocarbyl portion of a heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylhydrocarbyloxycarbonyl, or heterocyclohydrocarbyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle that contains one to four hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one or more carbon atoms by a halogen, alkyl, alkoxy, oxo group, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by an hydrocarbyl, arylhydrocarbyloxycarbonyl, hydrocarbyloyl, aryl or arylhydrocarbyl or on a tertiary nitrogen atom (i.e. =N-) by oxido and that is attached via a carbon atom.

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The tertiary nitrogen atom with three substituents can also form a N-oxide  $[=N^+(O)^-]$  group. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, and the like.

The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroarylhydrocarbyloyl (heteroarylhydrocarbyl carbonyl) group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle that contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. A "heteroaryl" group is an aromatic heterocyclic ring substituent that preferably contains one, or two, up to three or four, atoms in the ring other than carbon. Those heteroatoms can be nitrogen, sulfur or oxygen. A heteroaryl group can contain a single 5- or 6-membered ring or a fused ring system having two 6-membered rings or a 5- and a 6-membered ring. Exemplary heteroaryl groups include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-triazinyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl groups; 6-/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl and anthranilyl groups; and 6-/6-membered fused rings such as 1,2-, 1,4-, 2,3- and 2,1-benzopyronyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl groups.

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The term "cyclohydrocarbylhydrocarbyloxy-carbonyl" means an acyl group derived from a cyclohydrocarbylhydrocarbyloxy-carboxylic acid of the formula cyclohydrocarbylhydrocarbyl-O-COOH wherein cyclohydrocarbylhydrocarbyl has the significance given above. The term "aryloxyhydrocarbyloyl" means an acyl radical of the formula aryl-O-hydrocarbyloyl wherein aryl and hydrocarbyloyl have the significance given above. The term "heterocyclyloxy-carbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylhydrocarbyloyl" is an acyl radical derived from a heterocyclyl-substituted hydrocarbylcarboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylhydrocarbyloxy-carbonyl" means an acyl radical derived from a heterocyclyl-substituted hydrocarbyl-O-COOH wherein heterocyclyl has the significance given above. The term "heteroaryloxy-carbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above.

The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, hydrocarbyl, aryl, aralkyl, cyclohydrocarbyl, cyclohydrocarbylhydrocarbyl radicals and the like. The term "aminohydrocarbyloyl" means an acyl group derived from an amino-substituted hydrocarbyl-

-80-

carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents independently selected from hydrogen, alkyl, aryl, aralkyl, cyclohydrocarbyl, cyclohydrocarbylhydrocarbyl radicals and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine. The term "halohydrocarbyl" means a hydrocarbyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such halohydrocarbyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term perfluorohydrocarbyl means a hydrocarbyl group wherein each hydrogen has been replaced by a fluorine atom. Examples of such perfluorohydrocarbyl groups, in addition to trifluoromethyl above, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

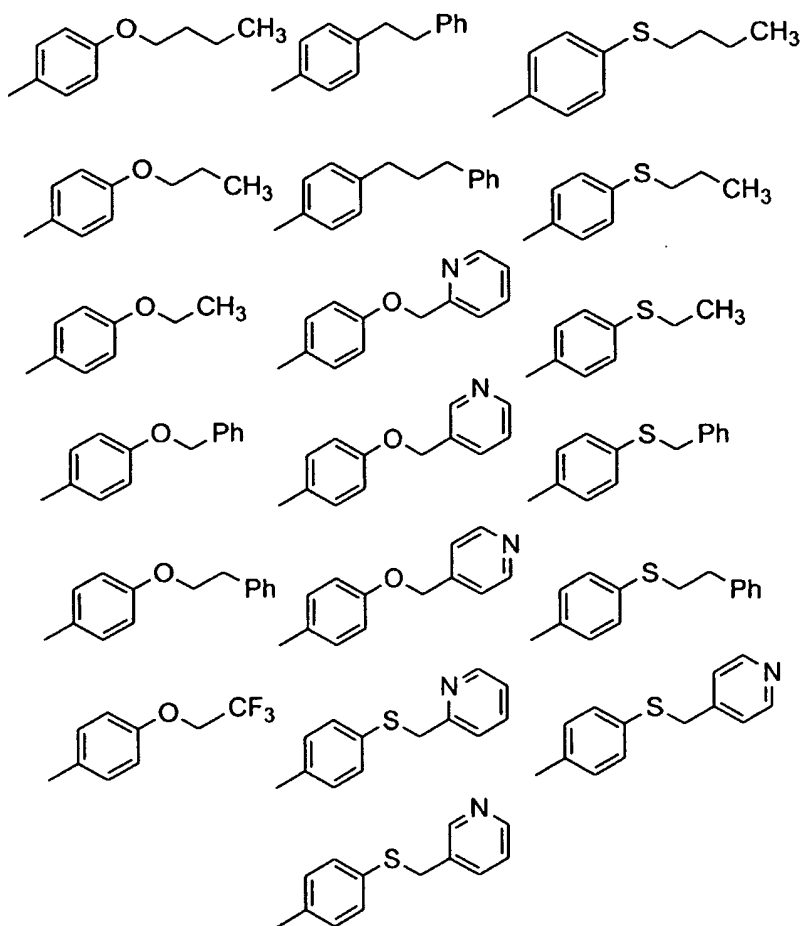
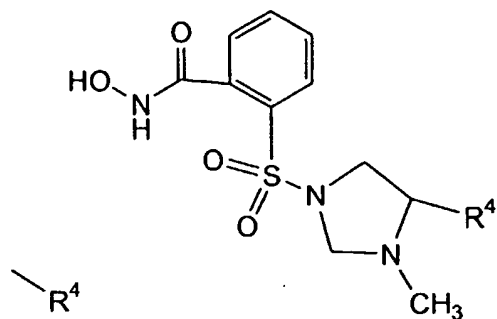
Table 1 through Table 88, below, show several contemplated sulfonyl aryl or heteroaryl hydroxamic acid compounds as structural formulas that illustrate substituent groups. Each group of compounds of Tables 1 through 70 is illustrated by a generic formula, followed by a series of preferred moieties or groups that constitute various substituents that can be attached at the position clearly shown in the generic structure. The substituent symbols, e.g.,  $R^1$ ,  $R^2$ , X, are as shown in each Table, and are often different from those shown elsewhere herein in structural formulas bearing Roman numerals of capital letters. One or two bonds (straight lines) are shown with those substituents to

-81-

indicate the respective positions of attachment in the illustrated compound. This system is well known in the chemical communication arts and is widely used in scientific papers and presentations. Tables 71  
5 through 88 illustrate specific compounds of the previous tables as well as other contemplated compounds using complete molecular formulas.

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Table 1





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Table 2

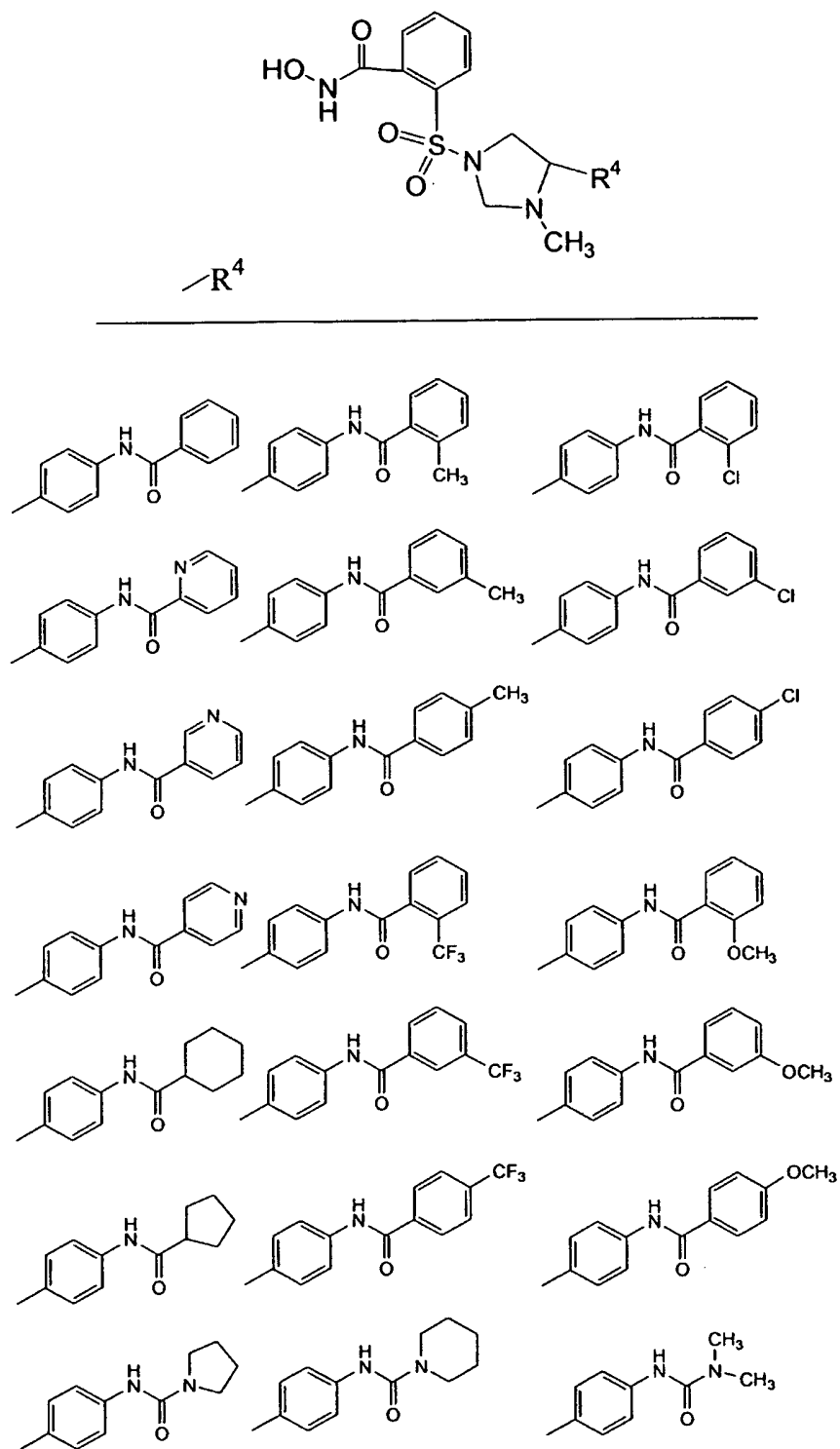


Table 3

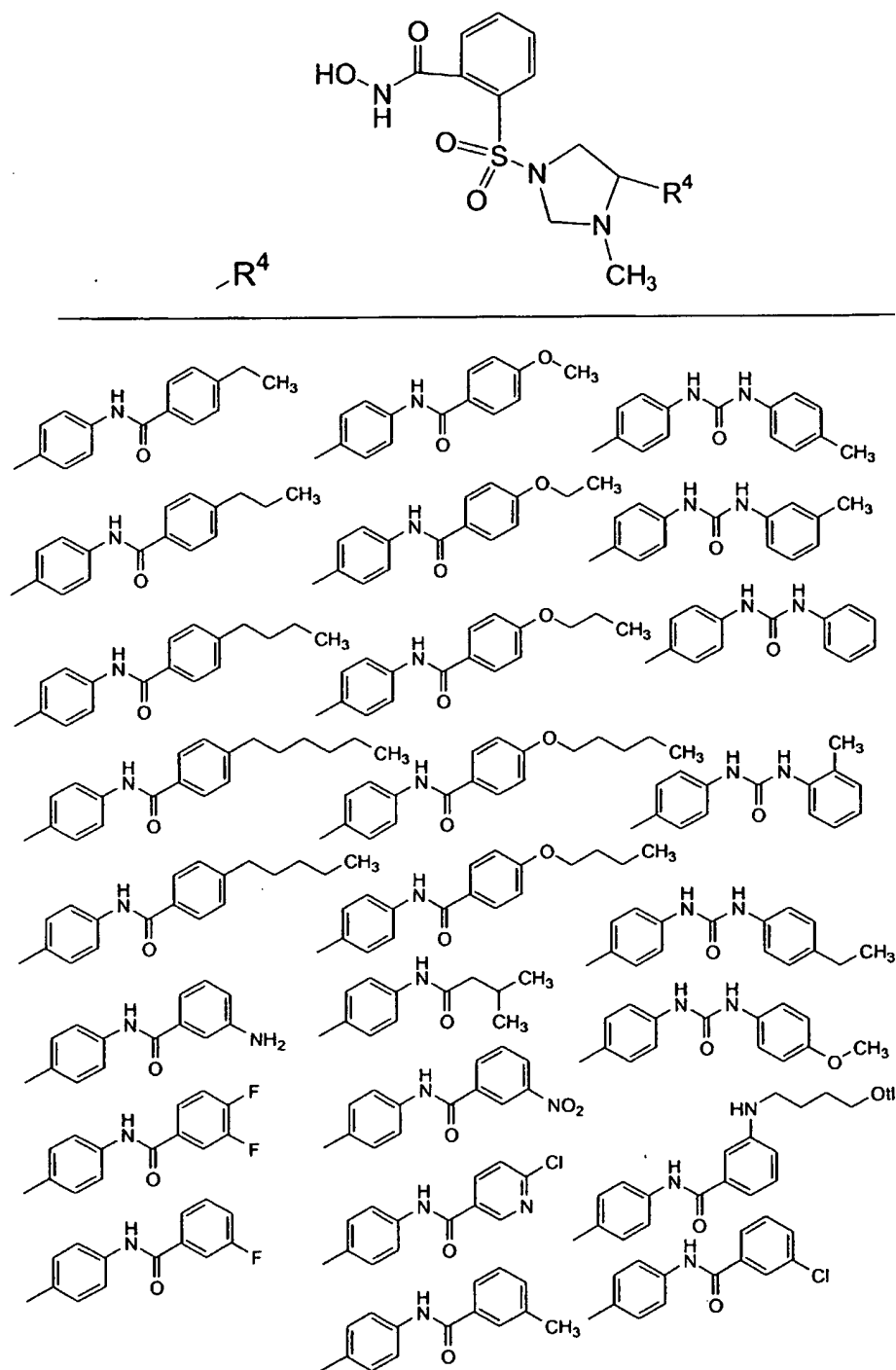


Table 4

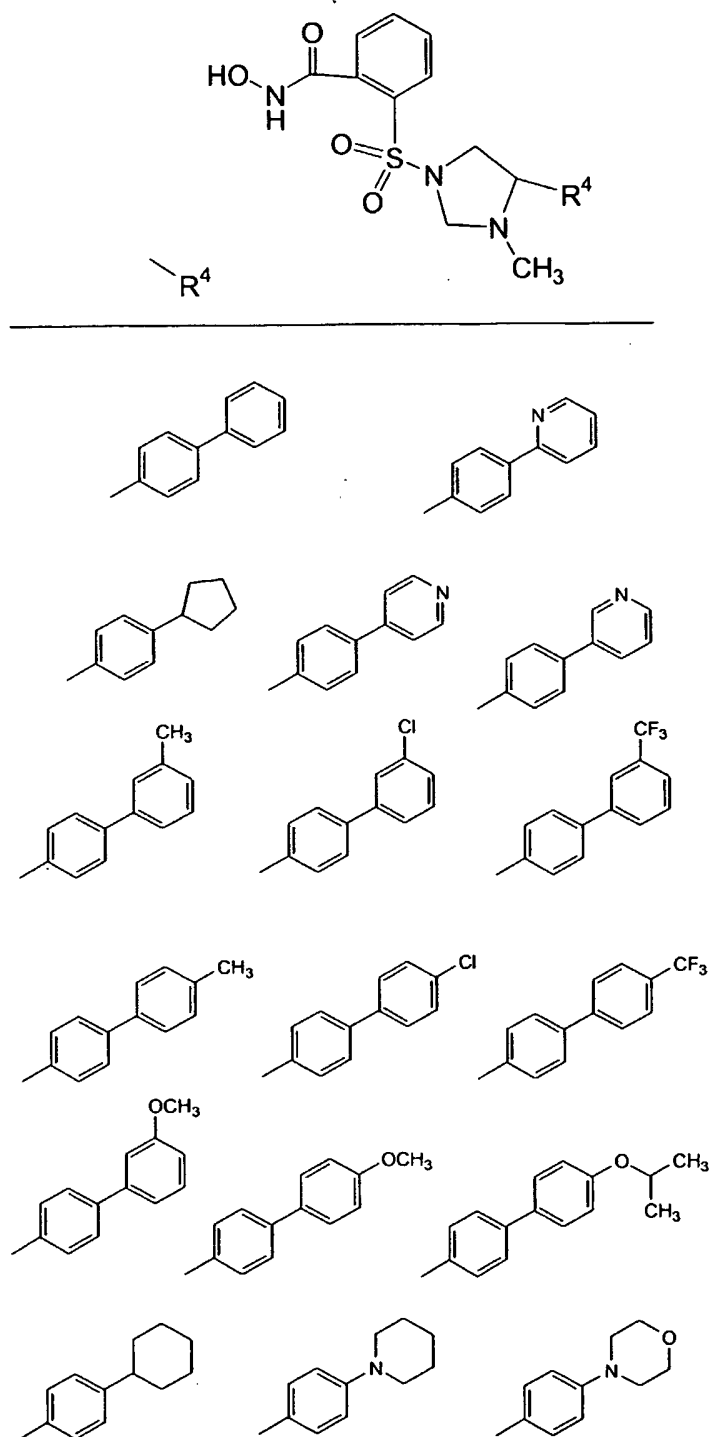
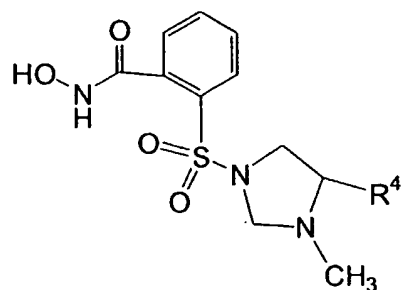
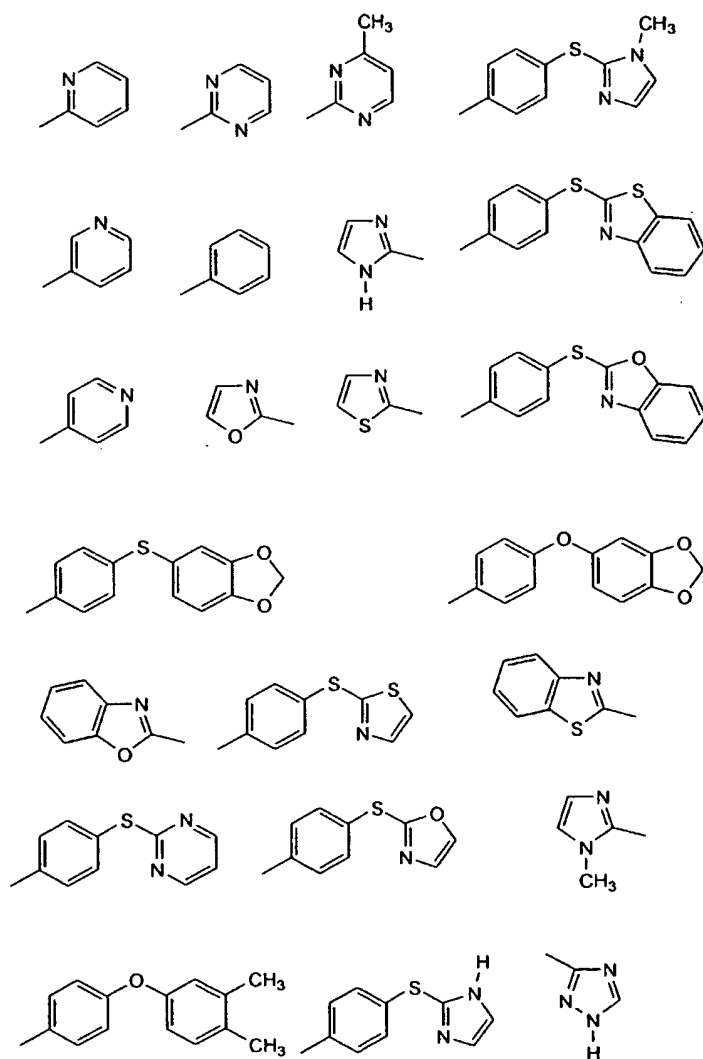
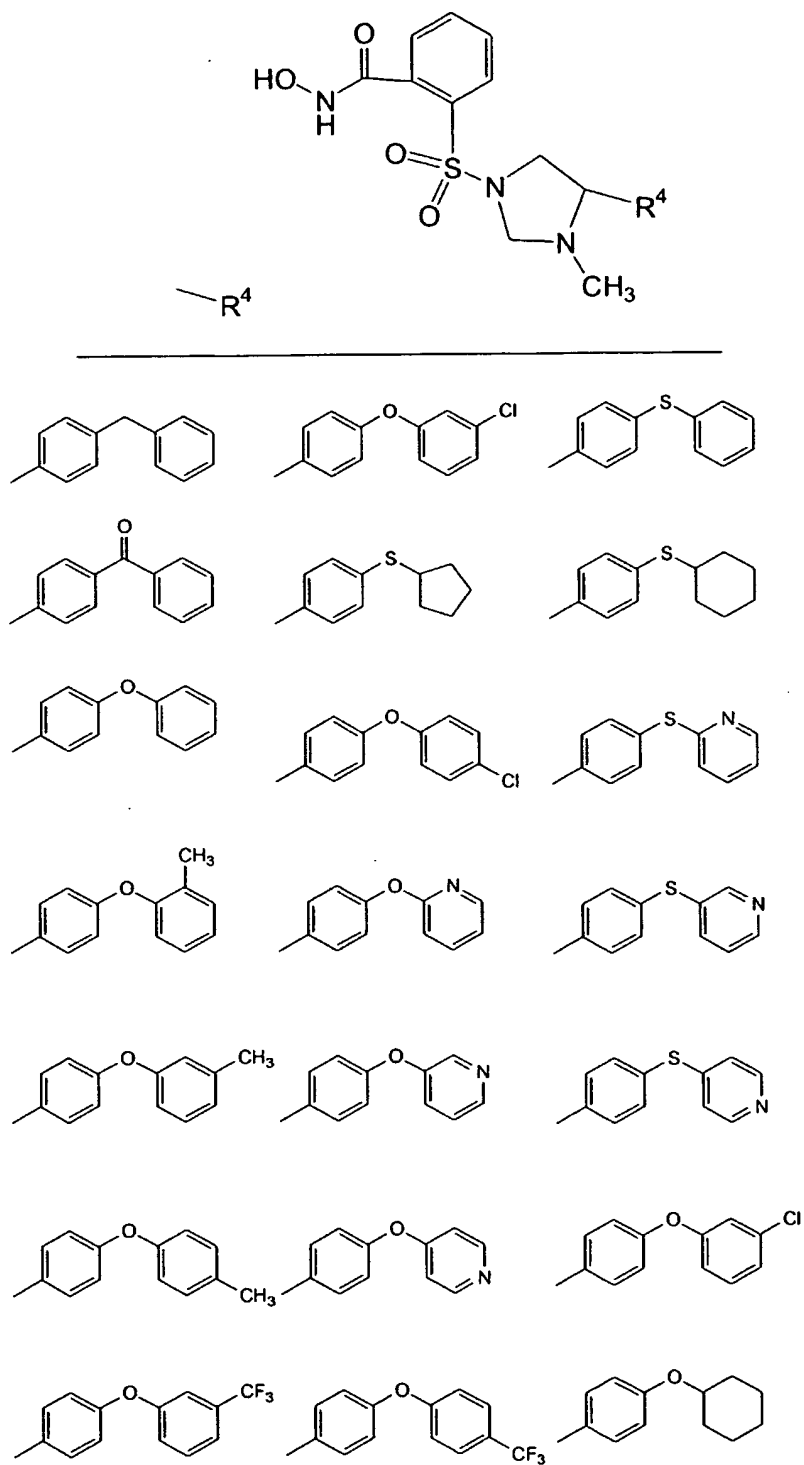


Table 5

 $\text{—R}^4$ 

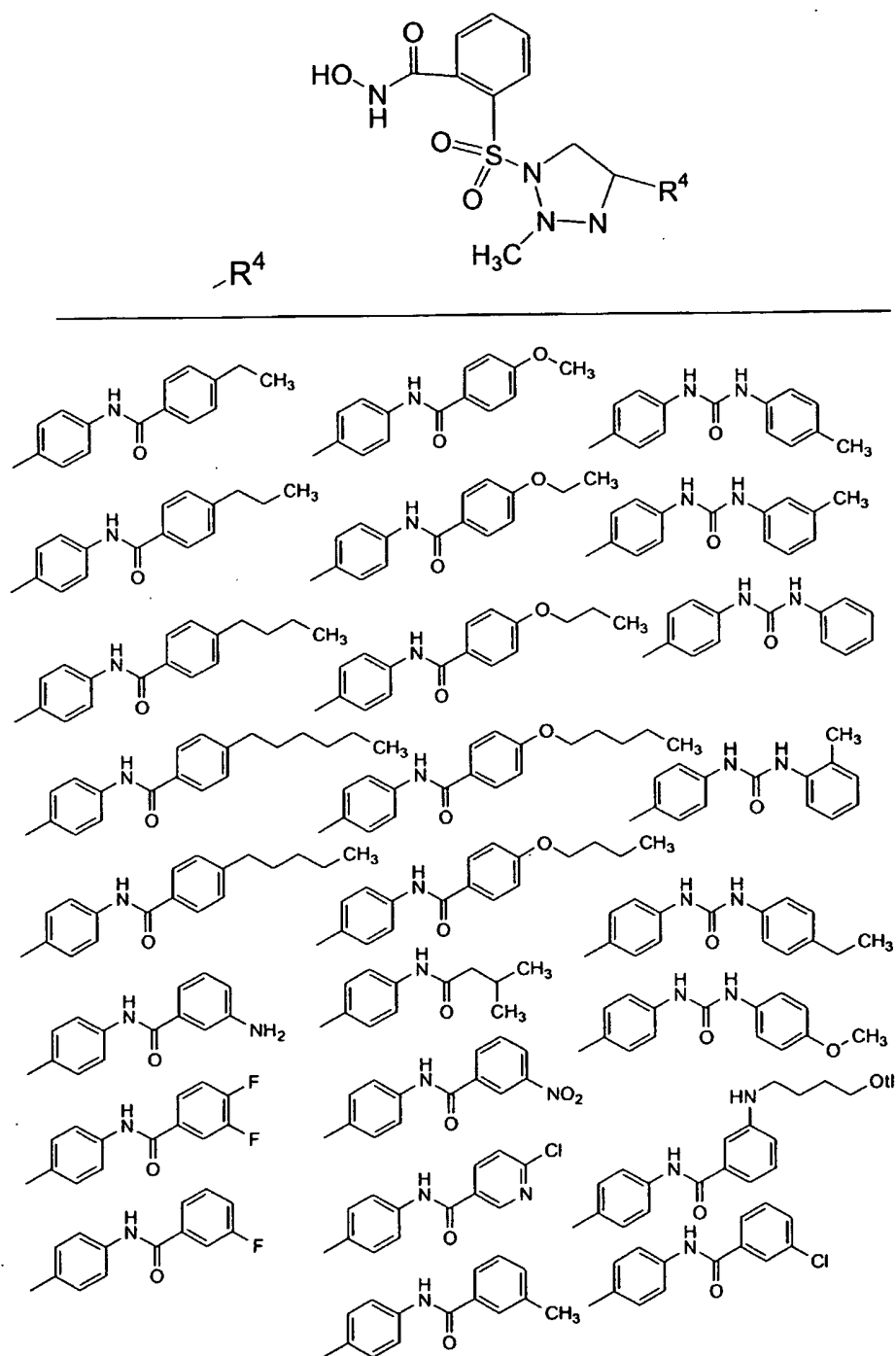
- 87 -

Table 6



- 88 -

Table 7



- 89 -

Table 8

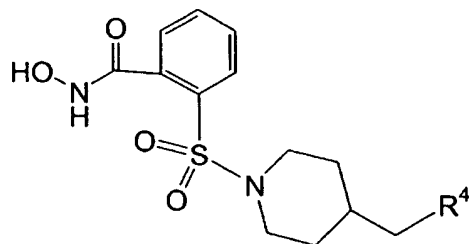
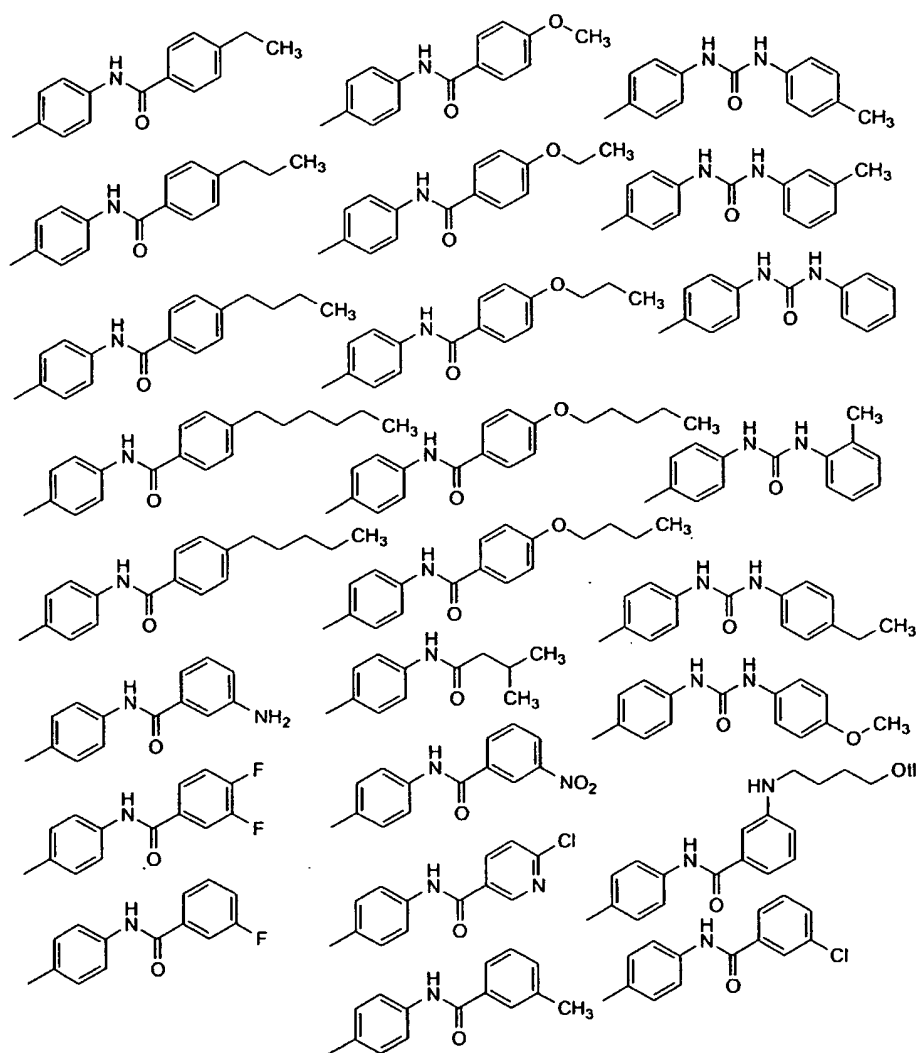
 $\text{R}^4$ 

Table 9

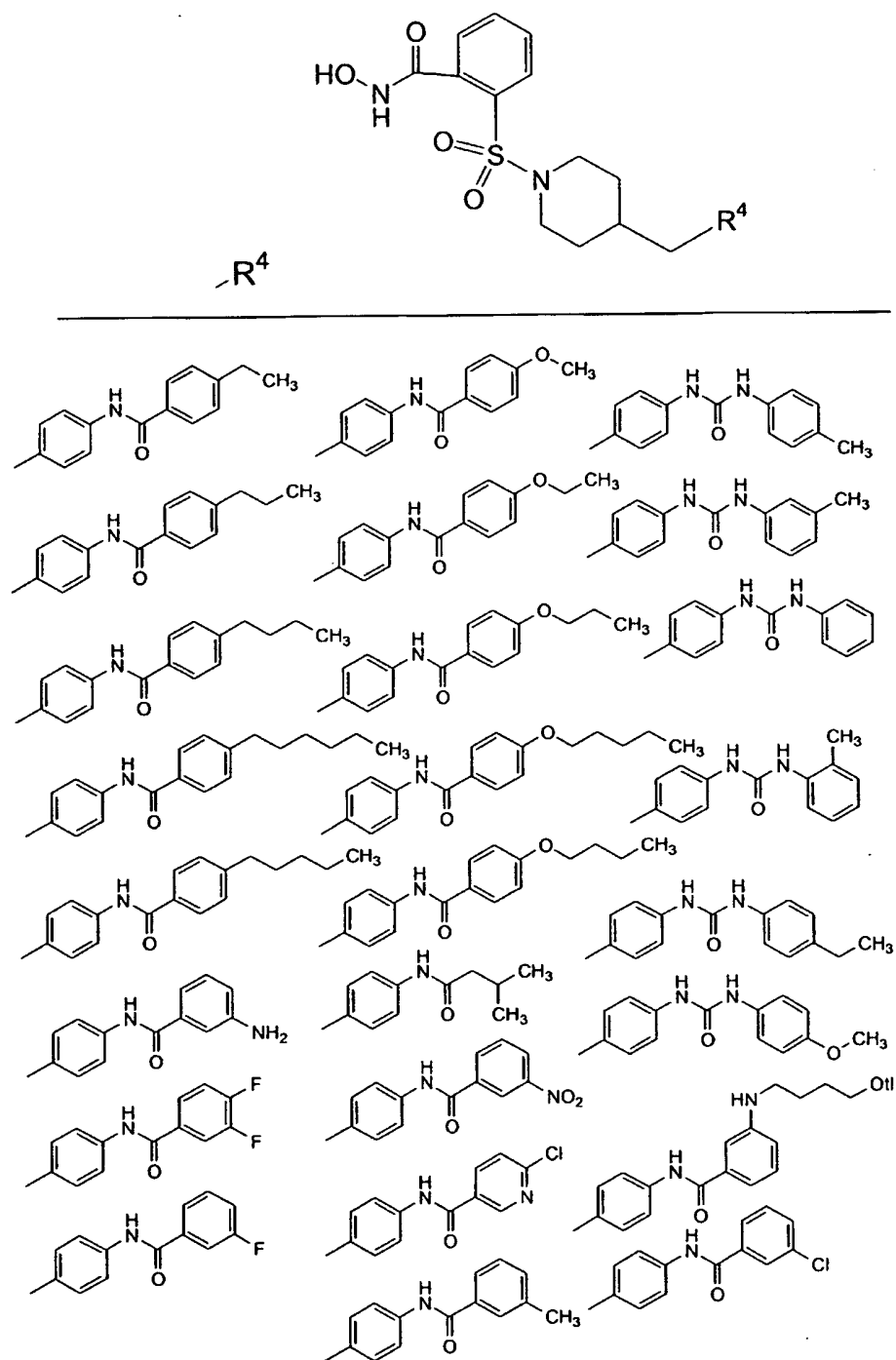
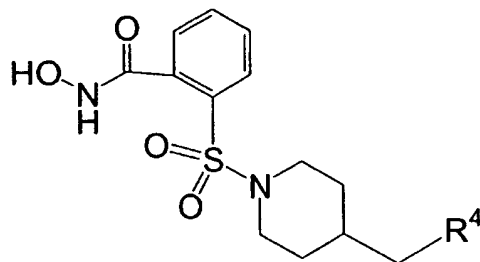


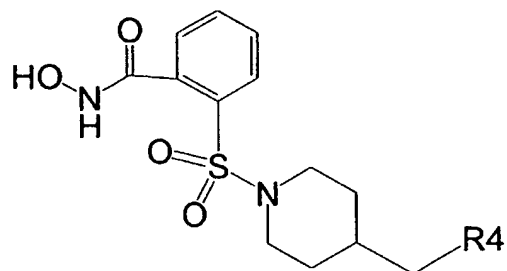


Table 10



Example	R <sup>4</sup>	Example	R <sup>4</sup>
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

Table 11



Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

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Table 12

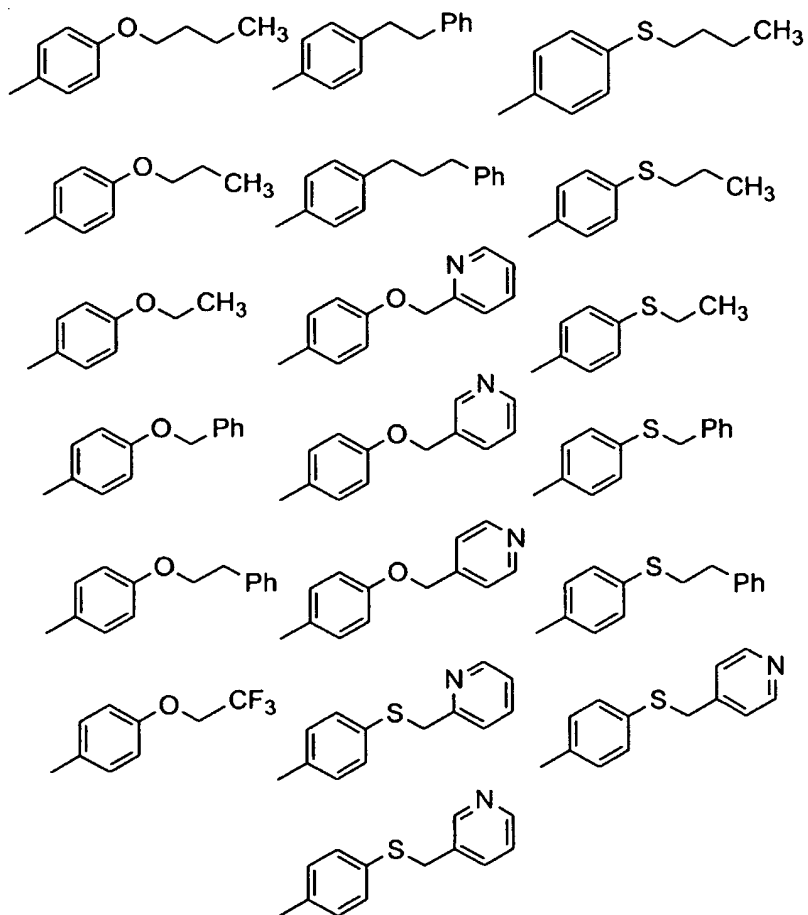
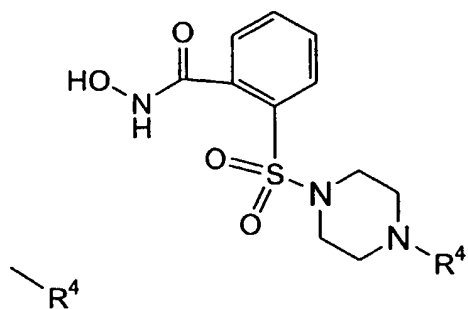


Table 13

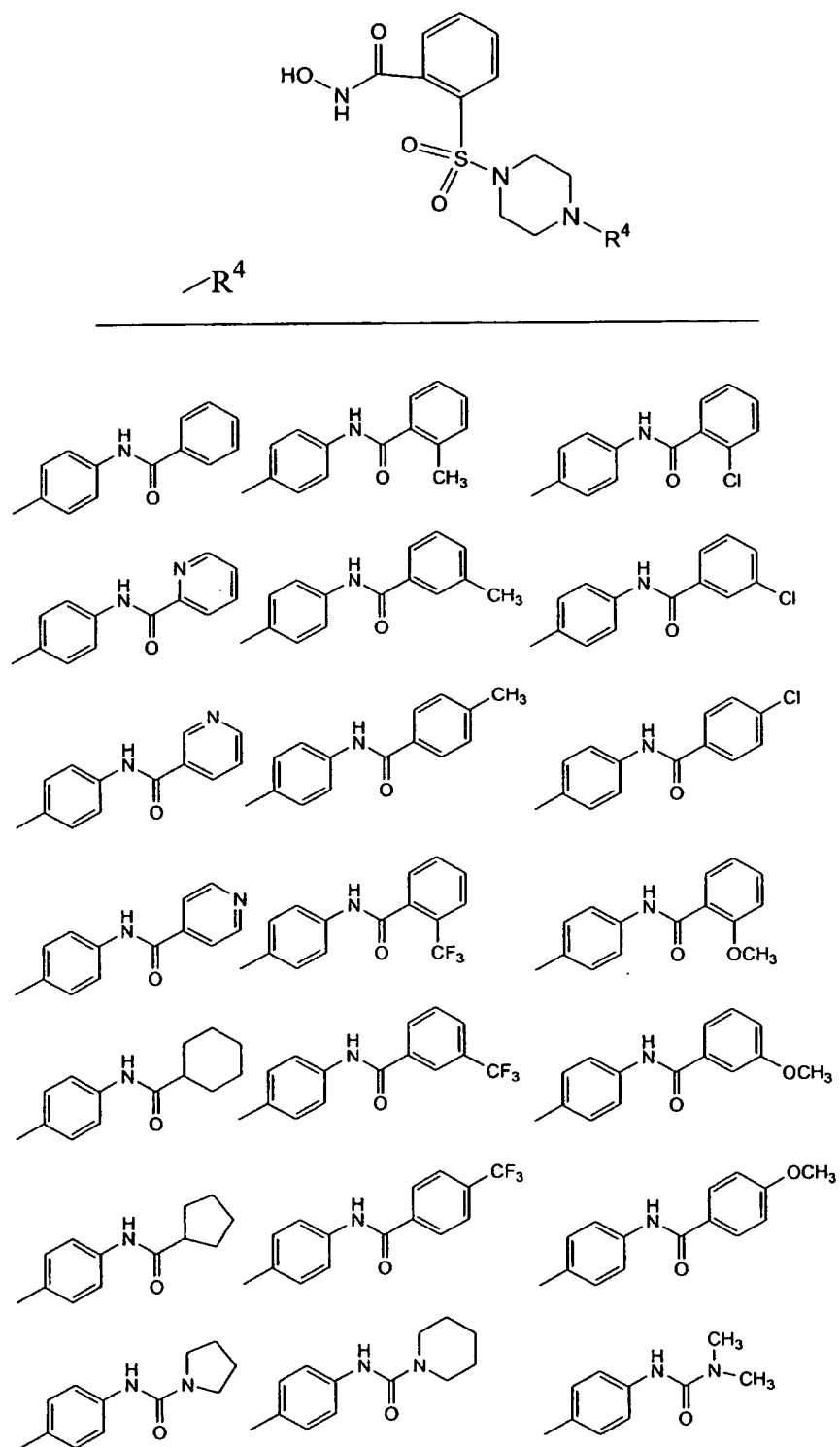
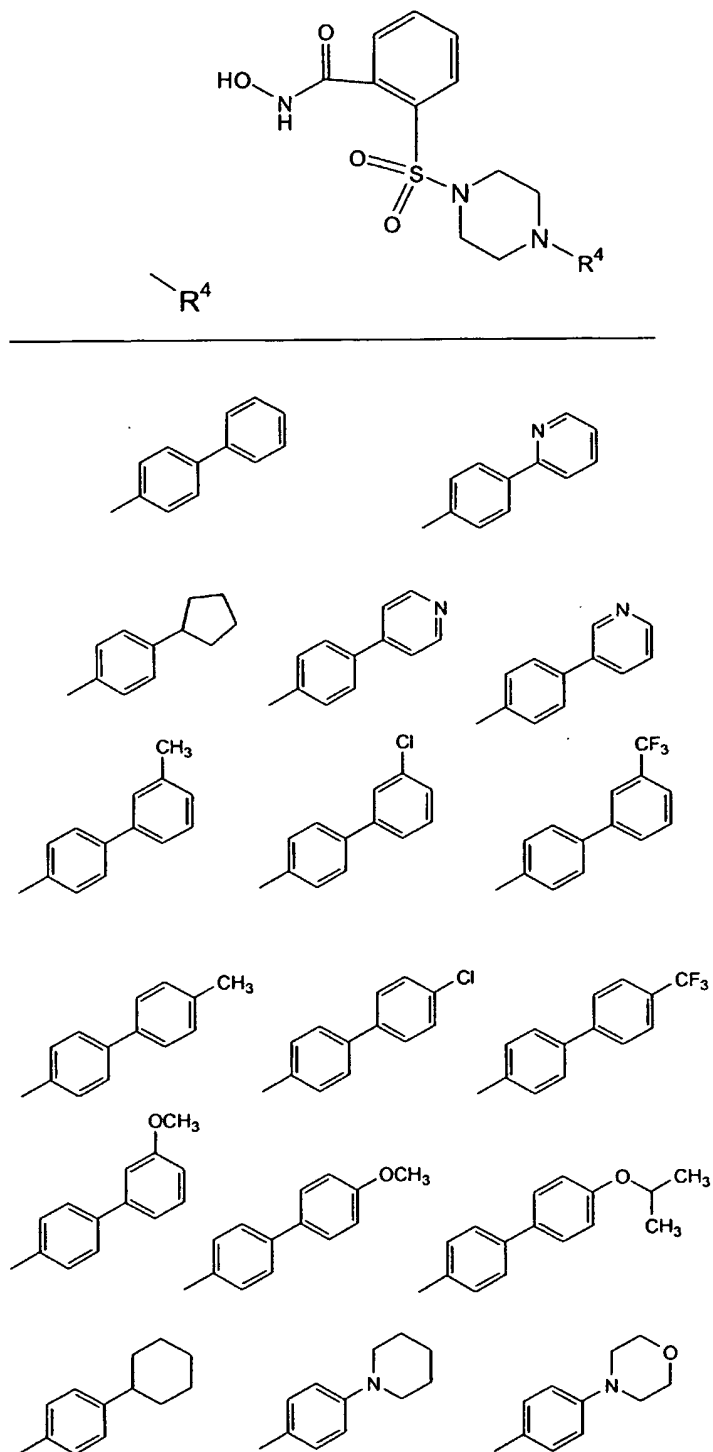


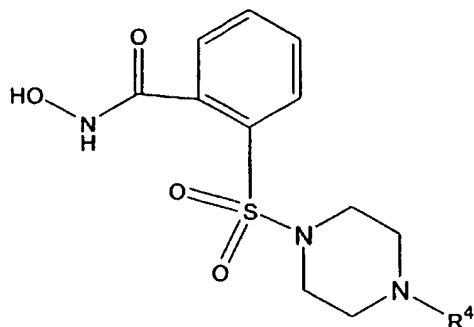
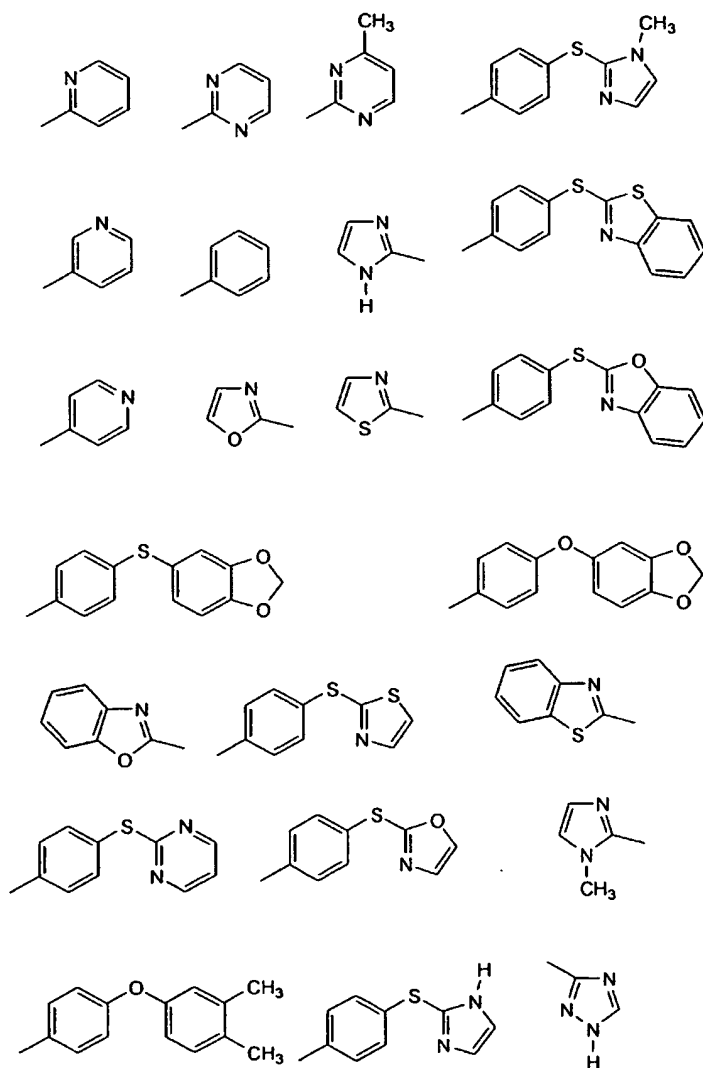


Table 15

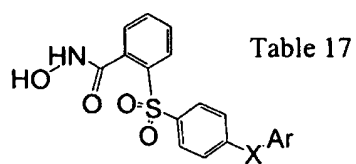


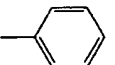
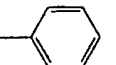
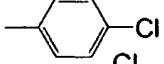
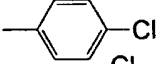
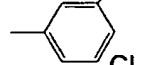
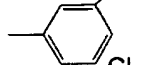
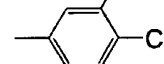
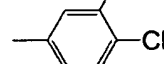
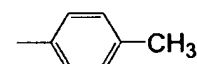
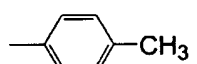
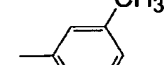
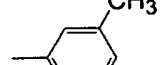
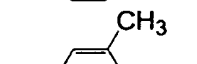
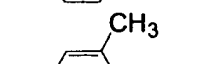
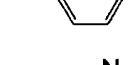
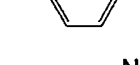
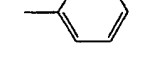
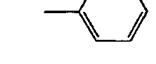
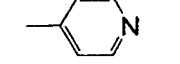
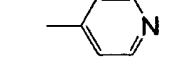
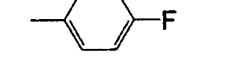
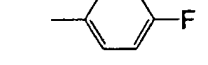
- 97 -

Table 16

 $\text{R}^4$ 

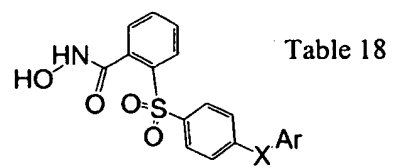
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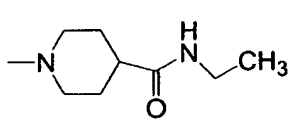
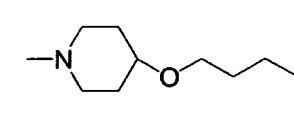
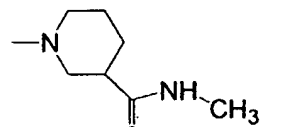
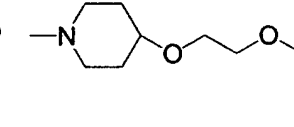
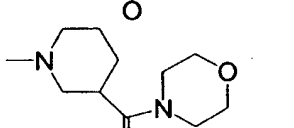
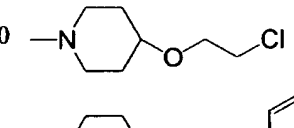
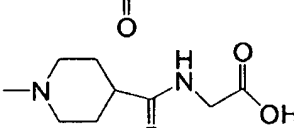
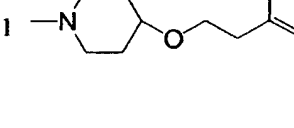
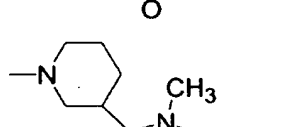
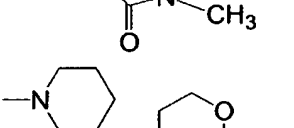
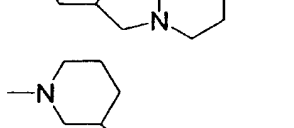


Example	X	Ar	Example	X	Ar
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2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

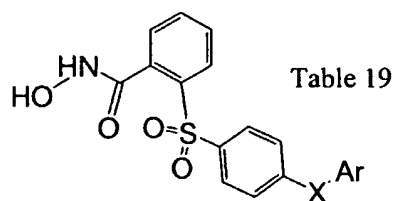


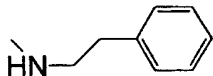
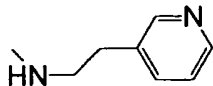
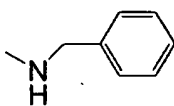
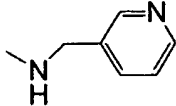
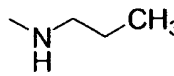
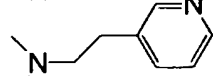
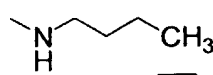
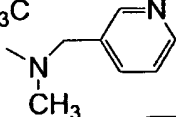
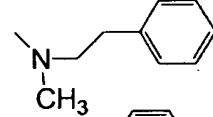
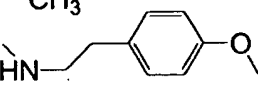
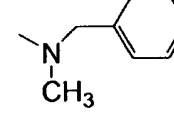
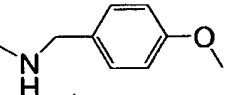
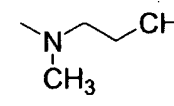
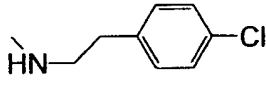
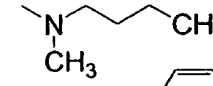
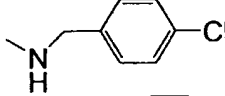
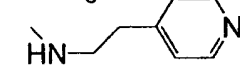
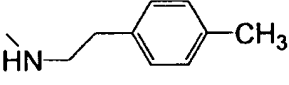
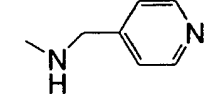
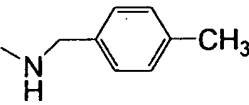
- 99 -



Example	X	Example	X
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

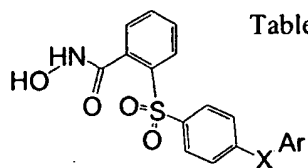
-100-



Example	X	Example	X
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

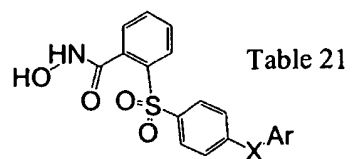
-101-

Table 20



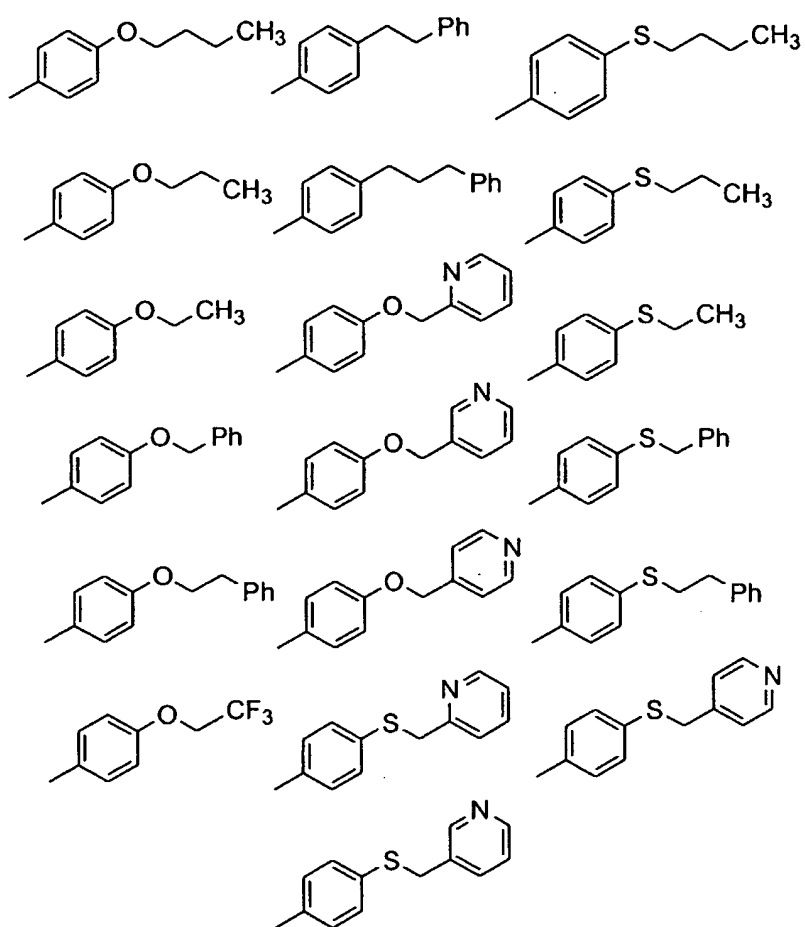
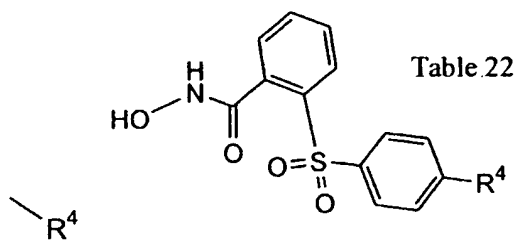
Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

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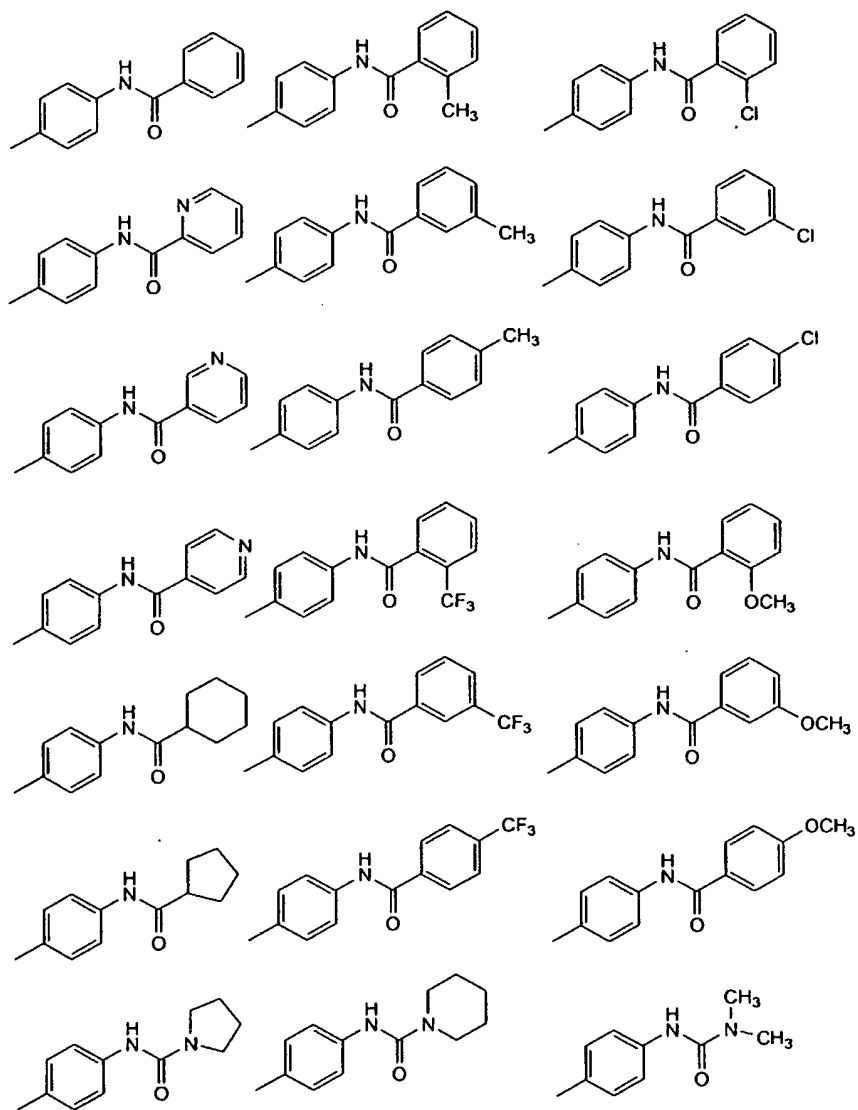
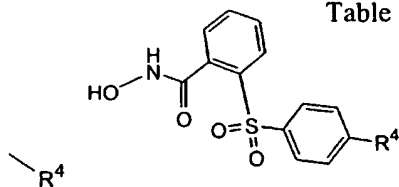
Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

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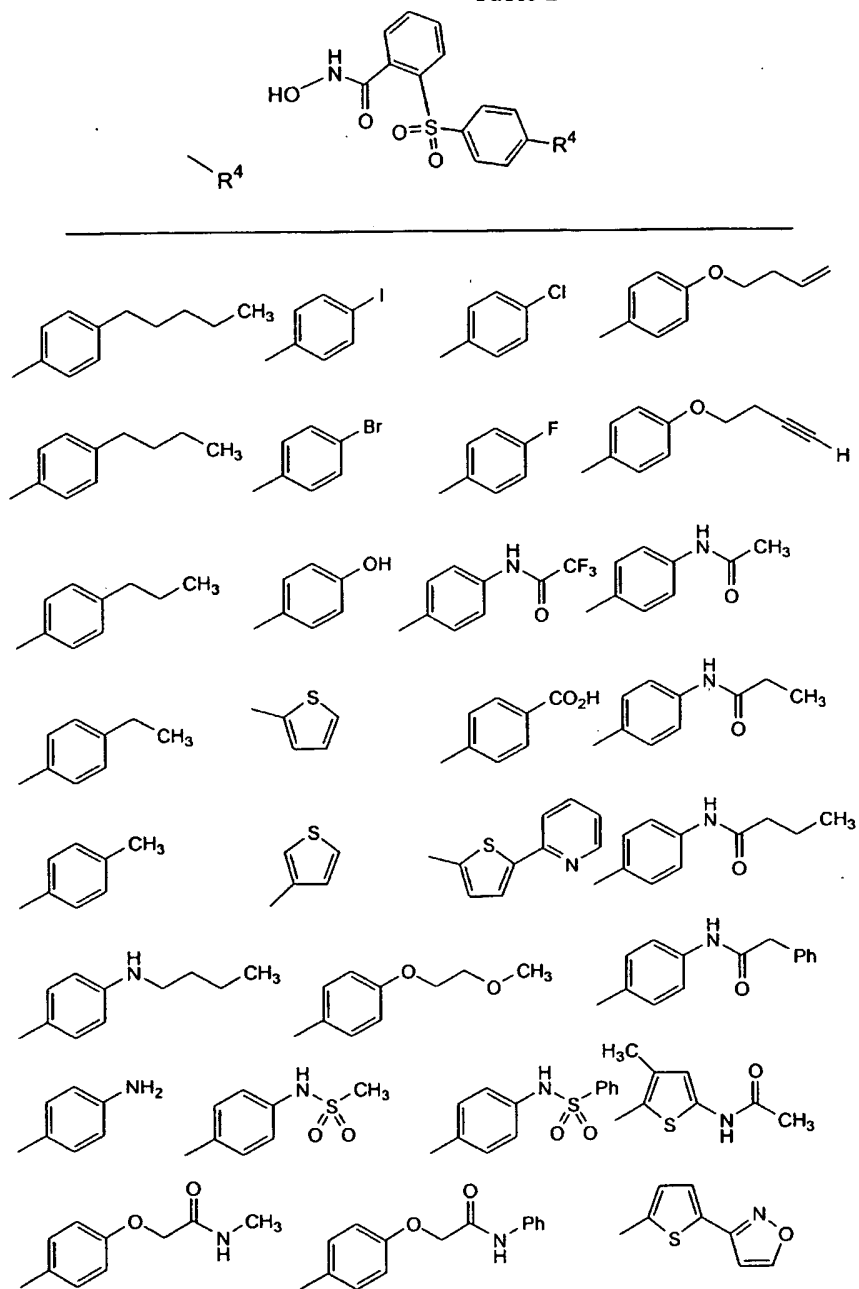
- 104 -

Table 23



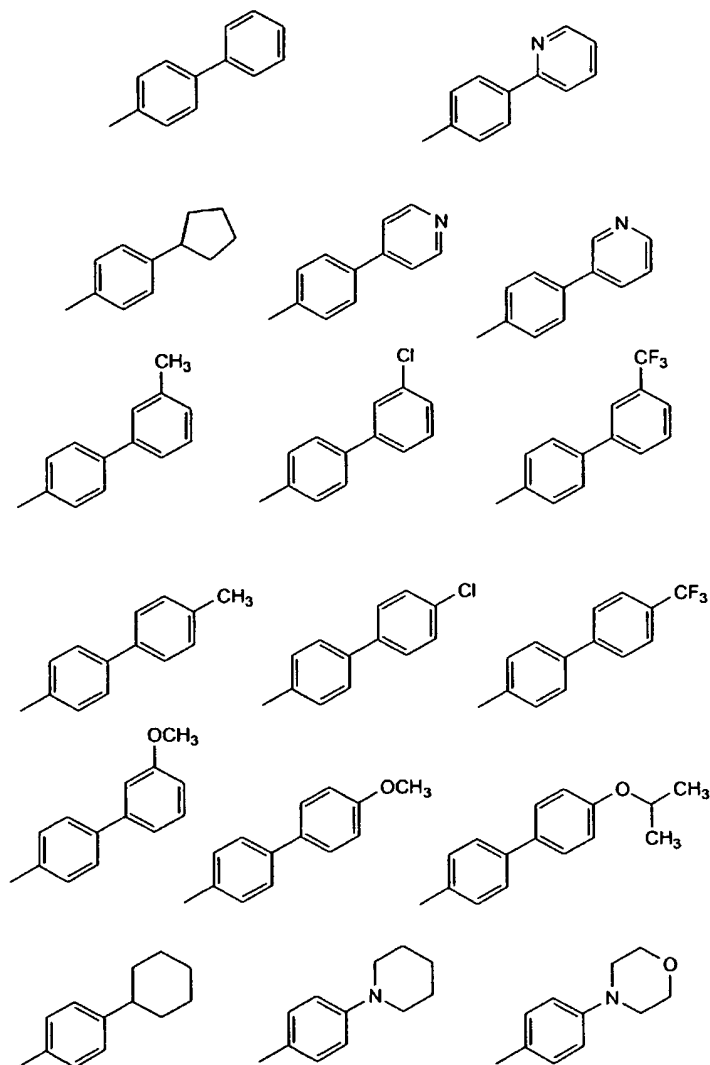
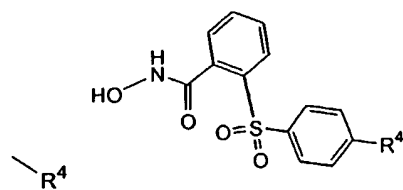
-105-

Table 24



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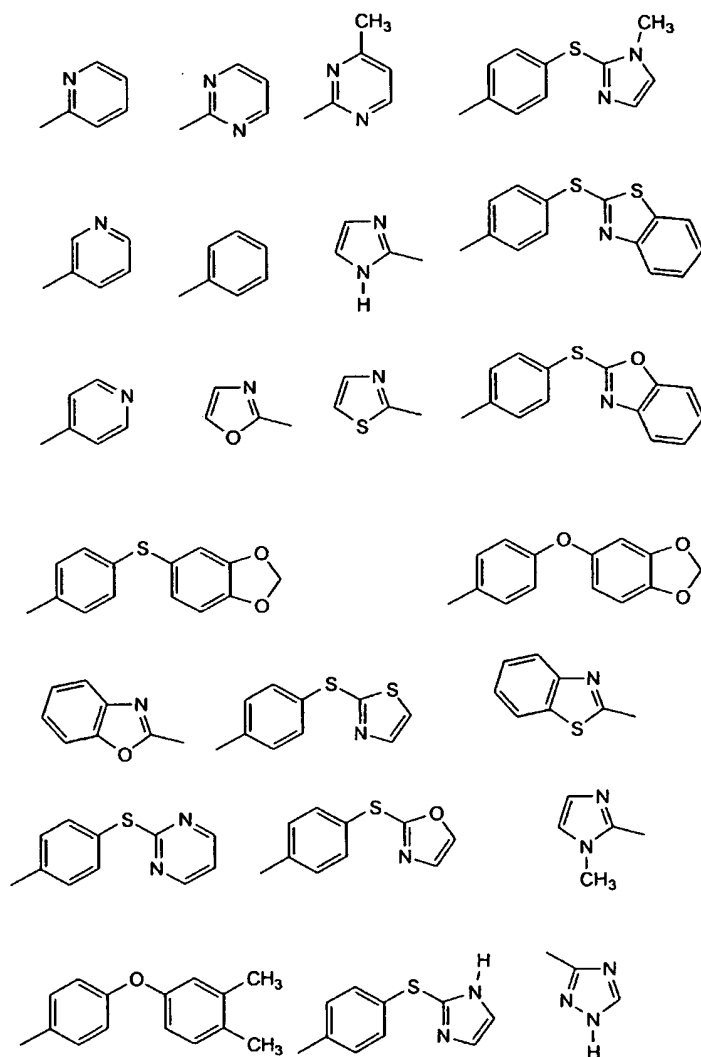
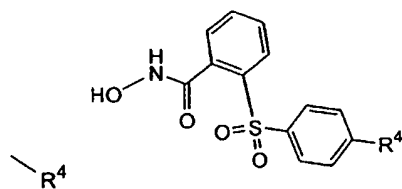
Table 25





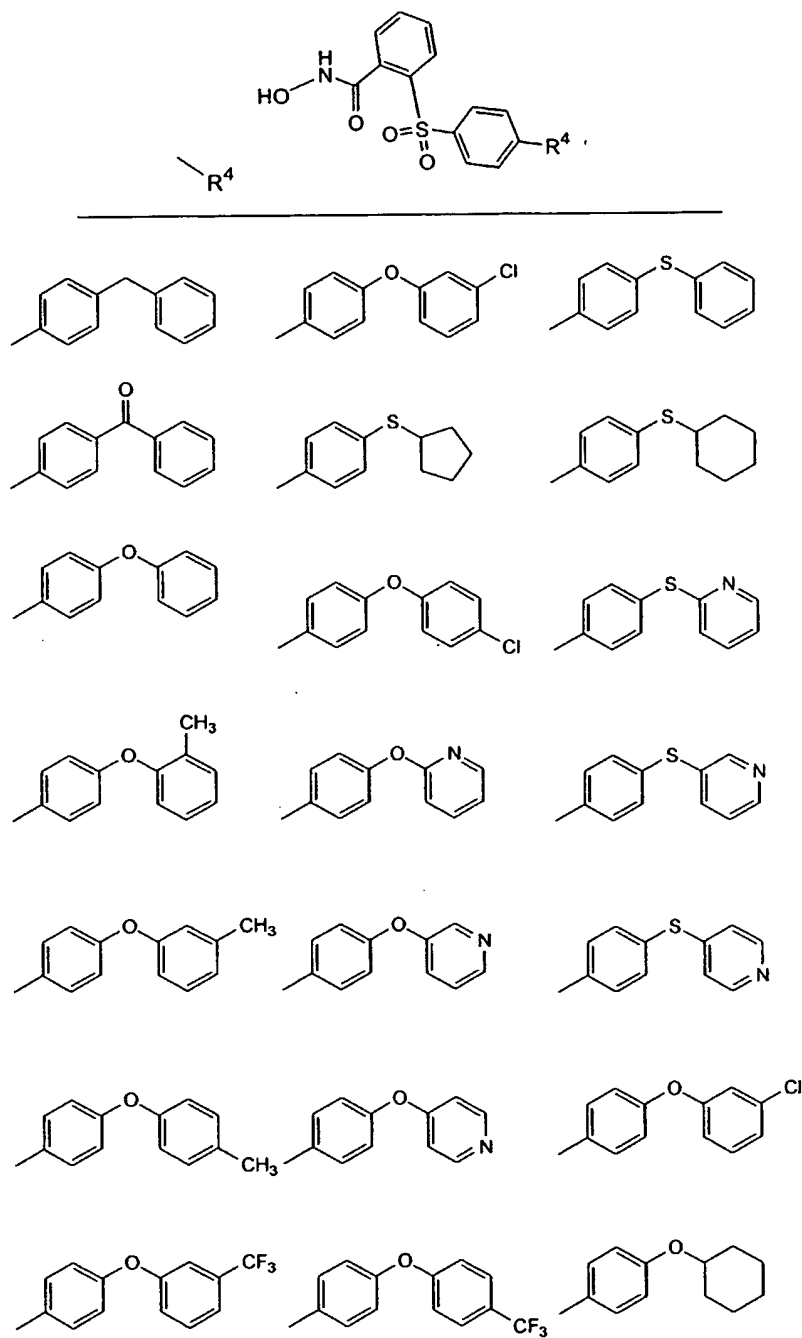
- 107 -

Table 26



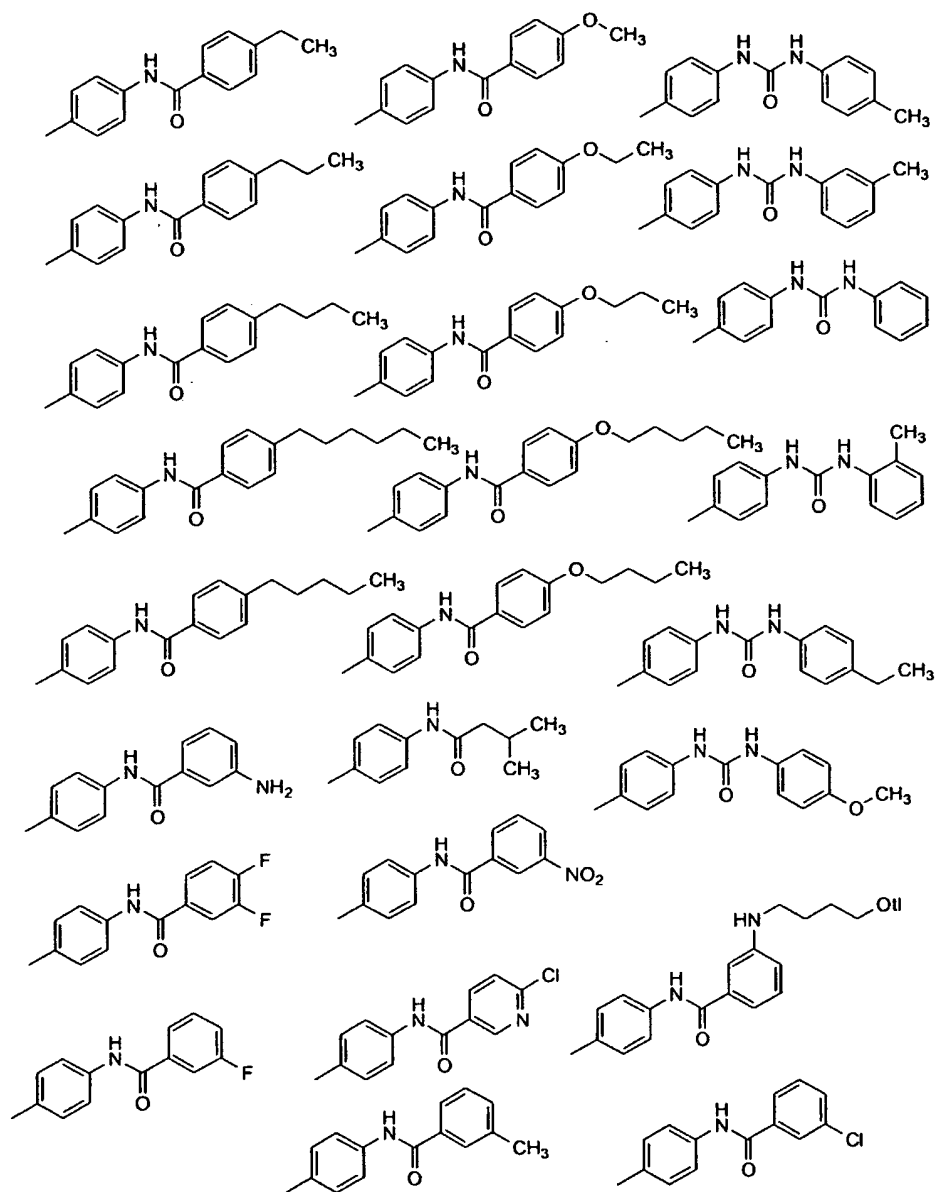
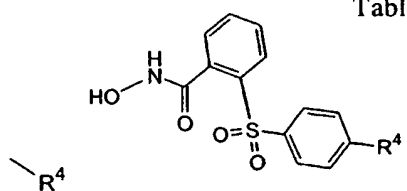
-108-

Table 27



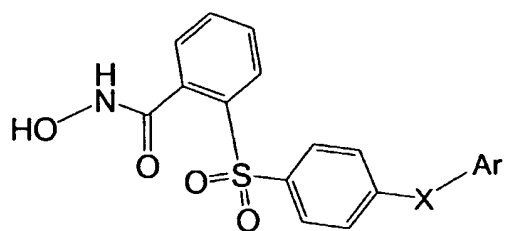
-109-

Table 28



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Table 29



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Example	X	Ar
1	O	
2	O	
3	S	
4	S	
5	S	
6	S	

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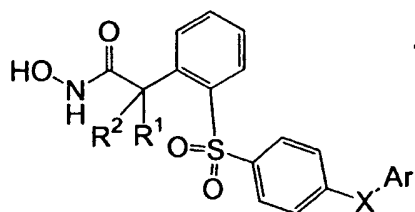
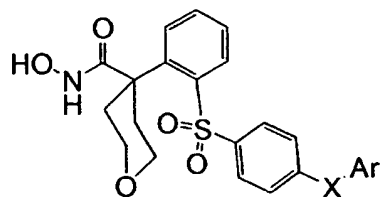


Table 30

Example	R <sup>1</sup>	R <sup>2</sup>	X	Ar
1			O	
2			O	
3			O	
4			O	
5			O	
6			O	
7			O	
8			O	
9			S	
10			S	
11			S	

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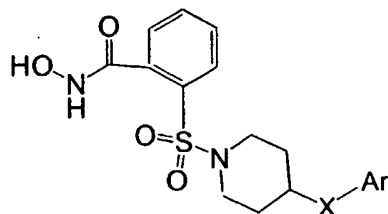
Table 31



Example	X	Ar
1	O	
2	O	
3	S	
4	S	
5	S	

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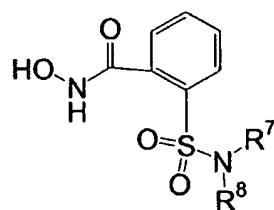
Table 32



Example	X	Ar	Example	X	Ar
1	O		12	S	
2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

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Table 33

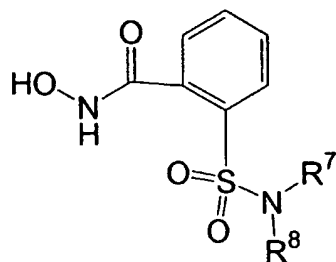


Example	$-\text{NR}^7\text{R}^8$	Example	$-\text{NR}^7\text{R}^8$
1		8	
2		9	
3		10	
4		11	
5			
6			
7			



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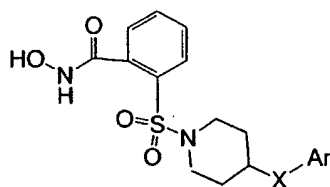
Table 34



Example	-NR <sup>7</sup> R <sup>8</sup>	Example	-NR <sup>7</sup> R <sup>8</sup>
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

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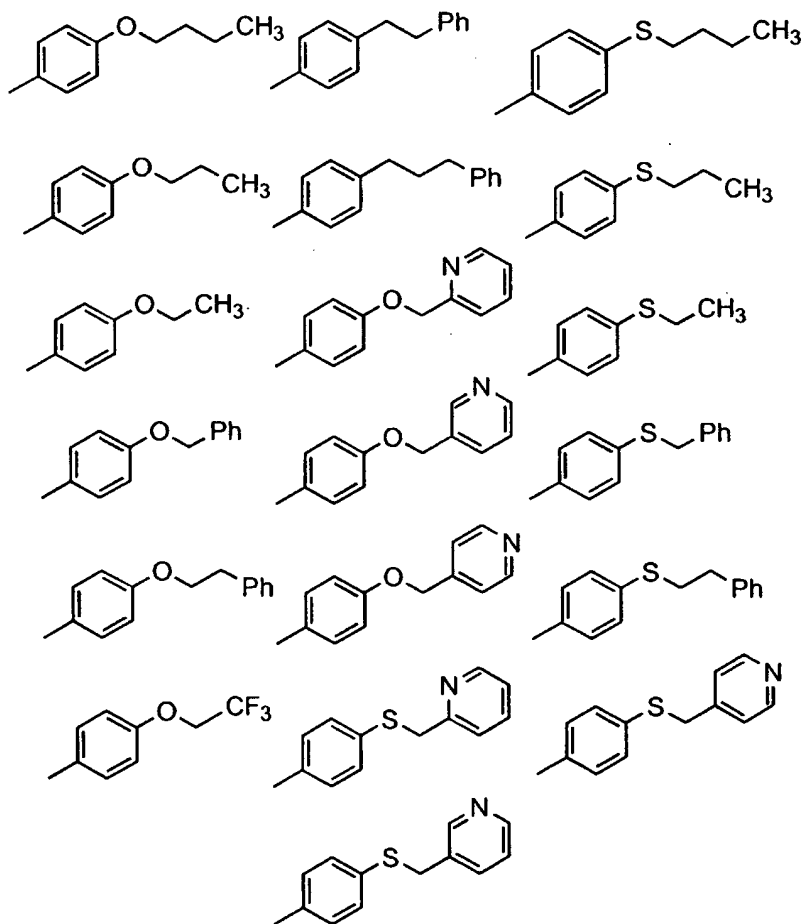
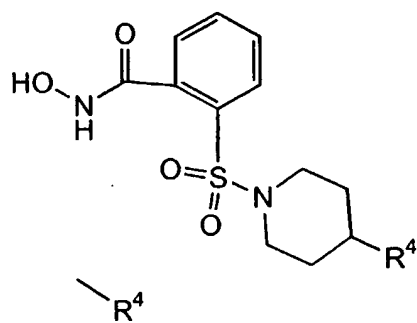
Table 35



Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

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Table 36



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Table 37

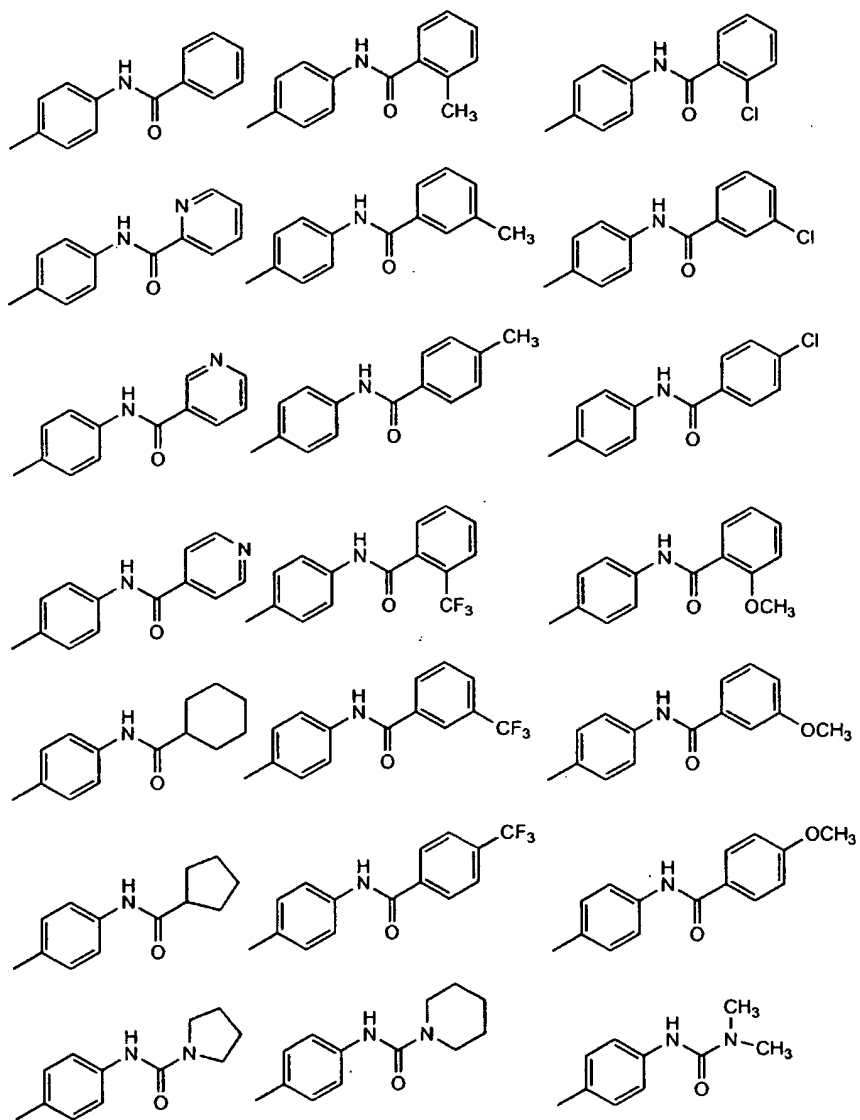
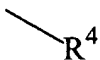
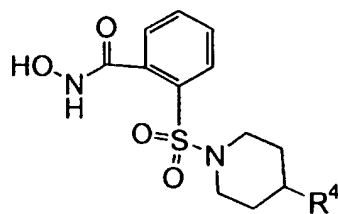
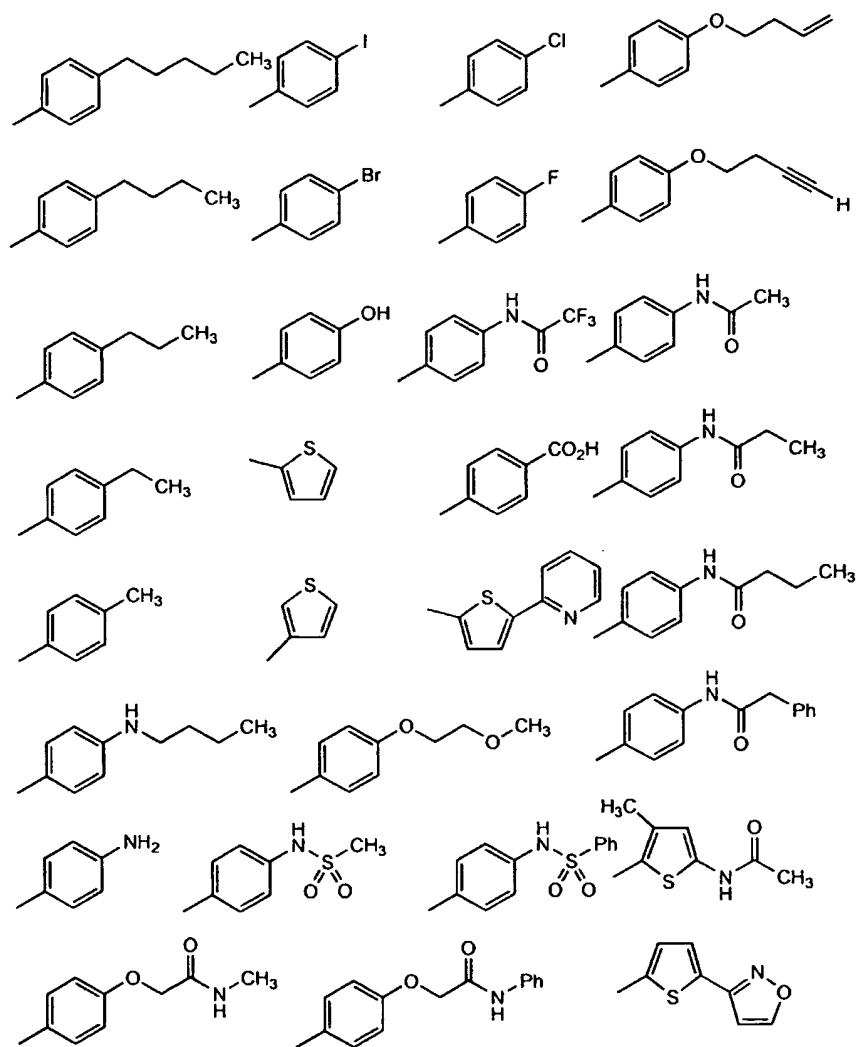
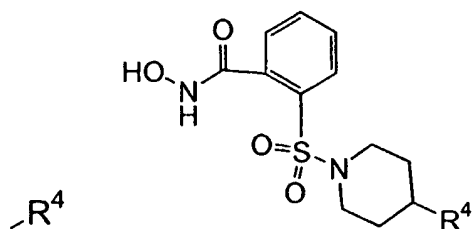
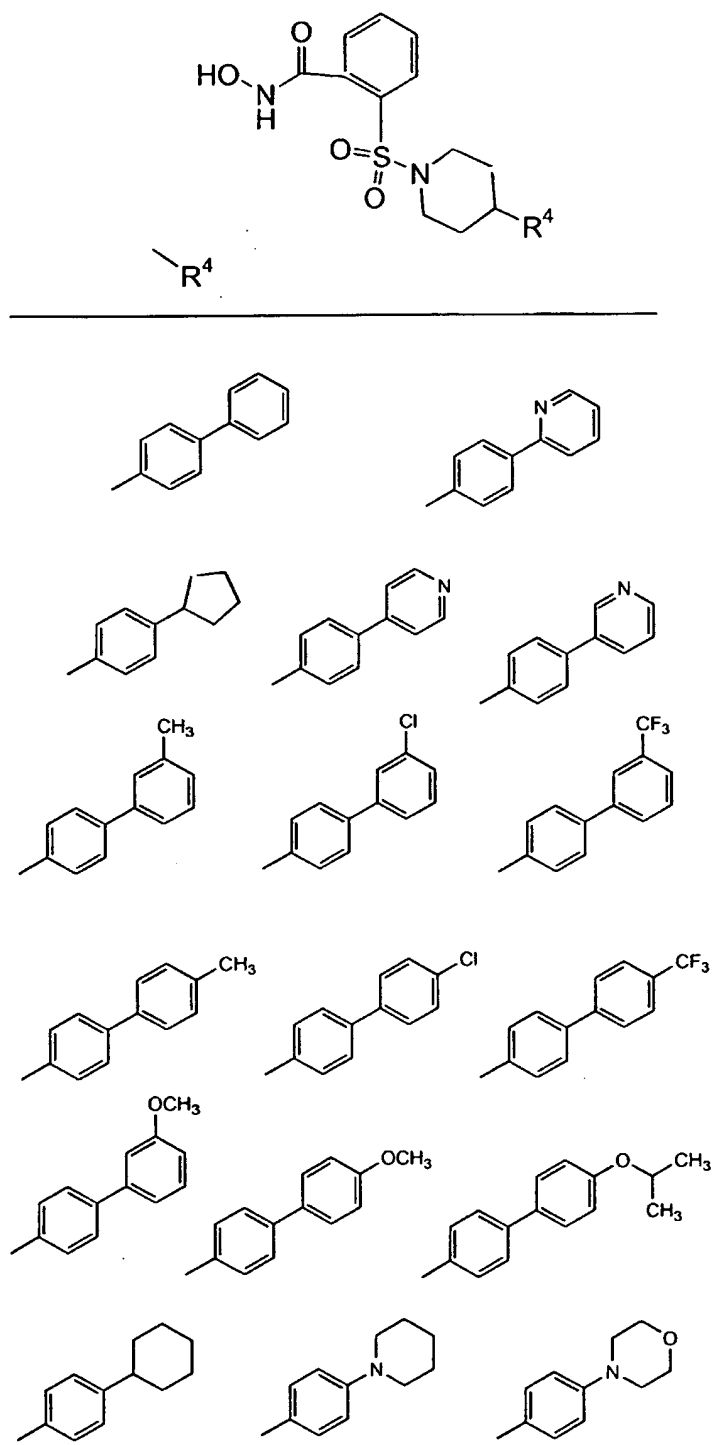


Table 38



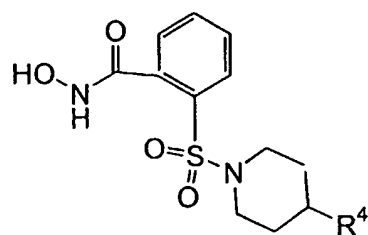
- 120 -

Table 39

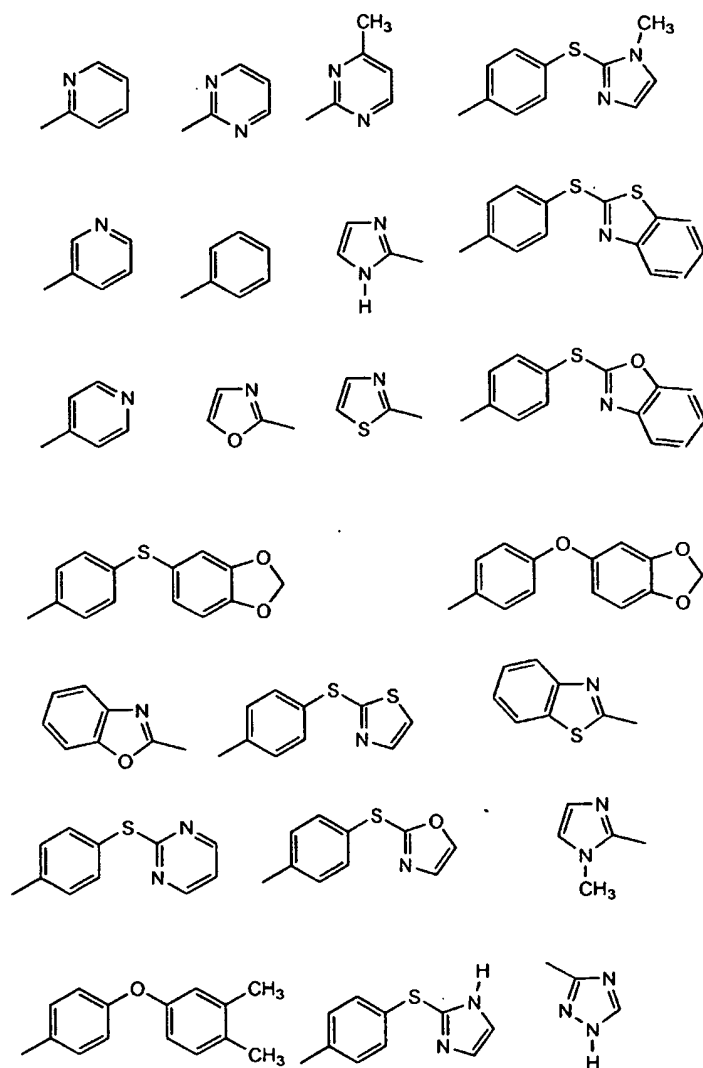


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Table 40

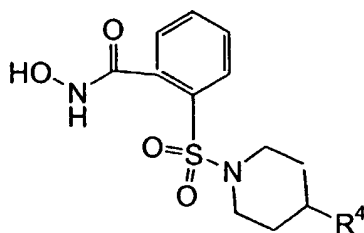


$\text{R}^4$

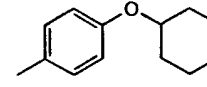
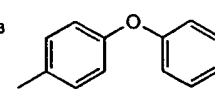
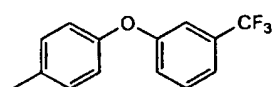
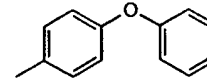
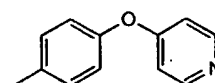
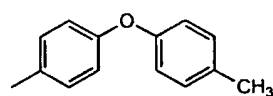
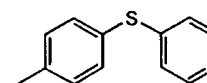
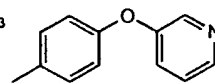
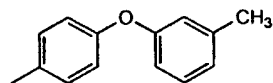
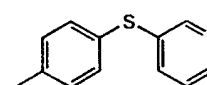
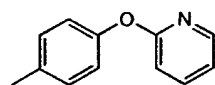
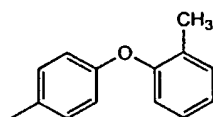
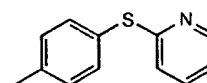
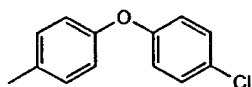
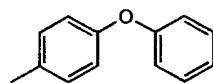
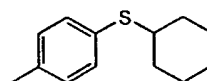
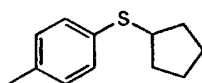
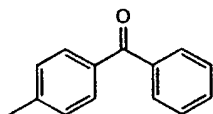
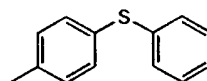
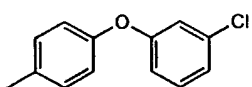
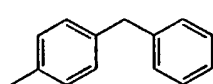


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Table 41



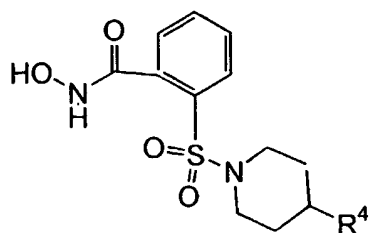
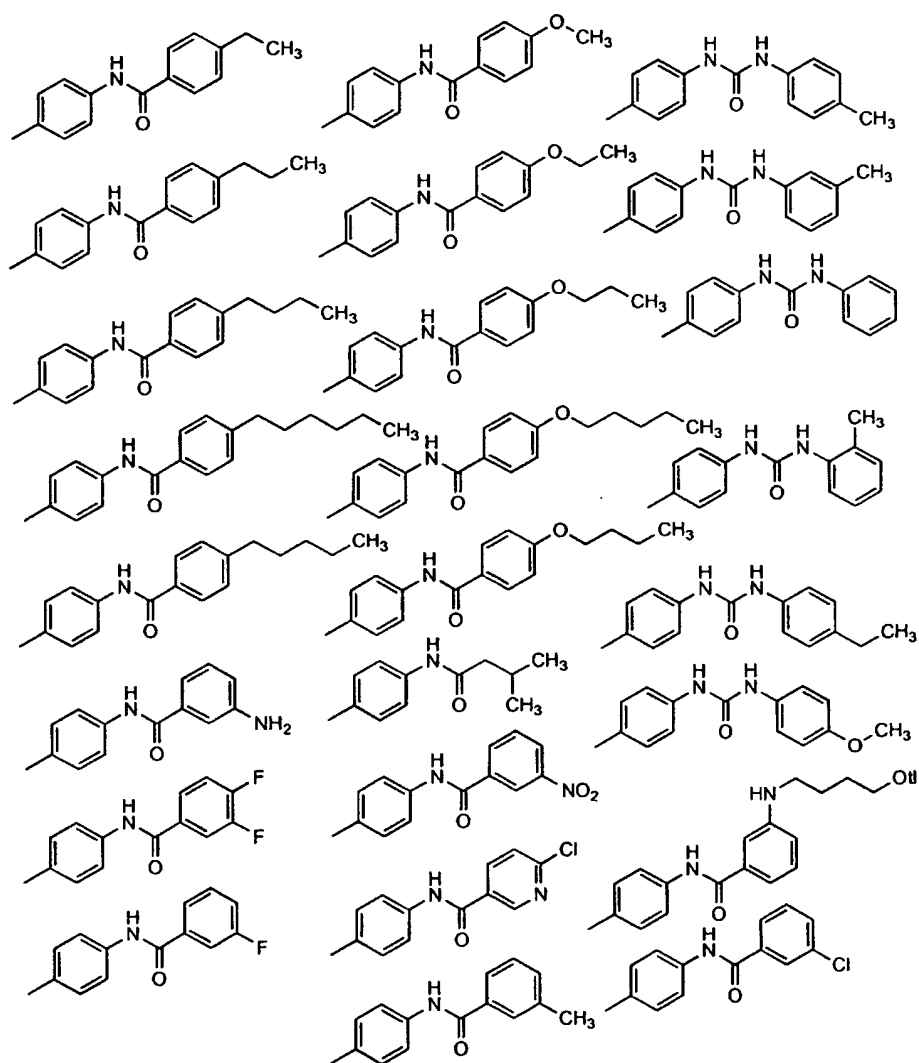
—R<sup>4</sup>





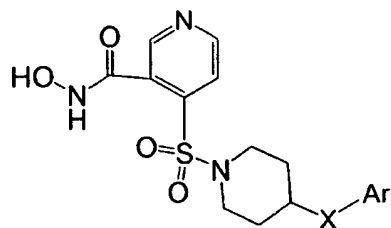
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Table 42

 $\mathbb{R}^4$ 

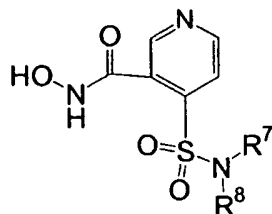
- 124 -

Table 43



Example	X	Ar	Example	X	Ar
1	O		12	S	
2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

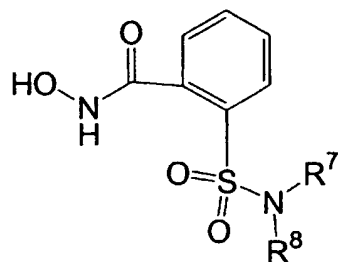
Table 44



Example	-NR <sup>7</sup> R <sup>8</sup>	Example	-NR <sup>7</sup> R <sup>8</sup>
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

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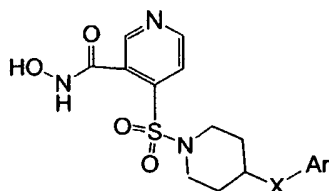
Table 45



Example	-NR <sup>7</sup> R <sup>8</sup>	Example	-NR <sup>7</sup> R <sup>8</sup>
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

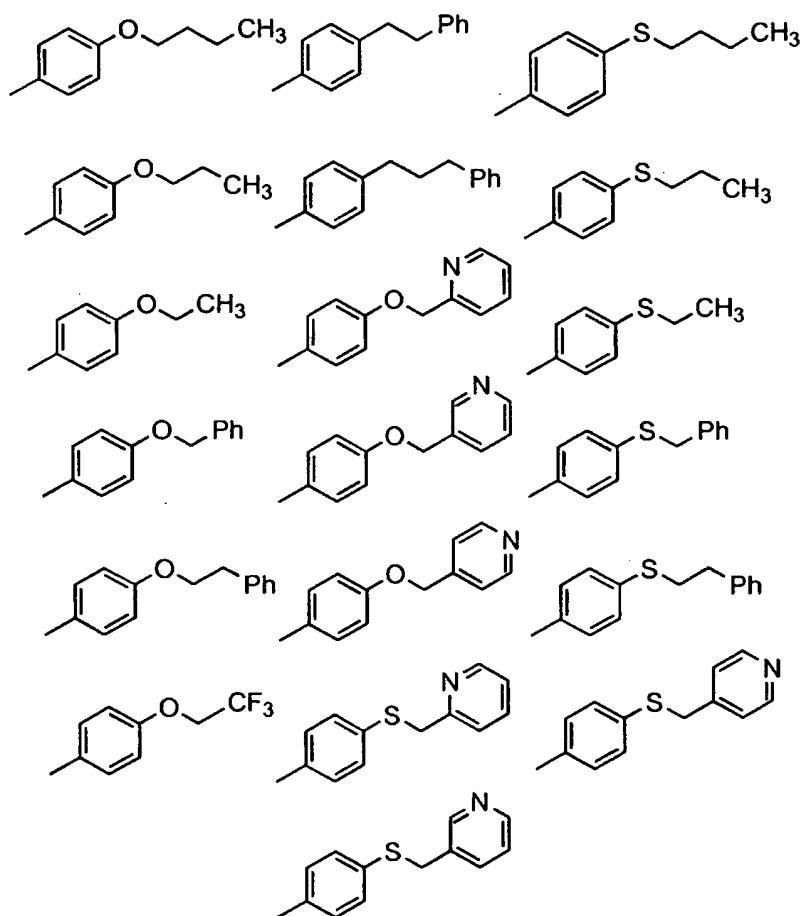
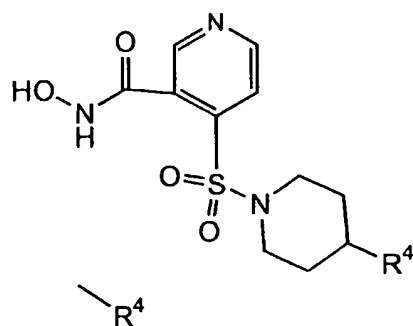
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Table 46



Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

Table 47



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Table 48

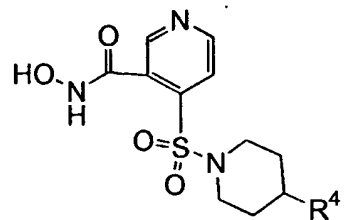
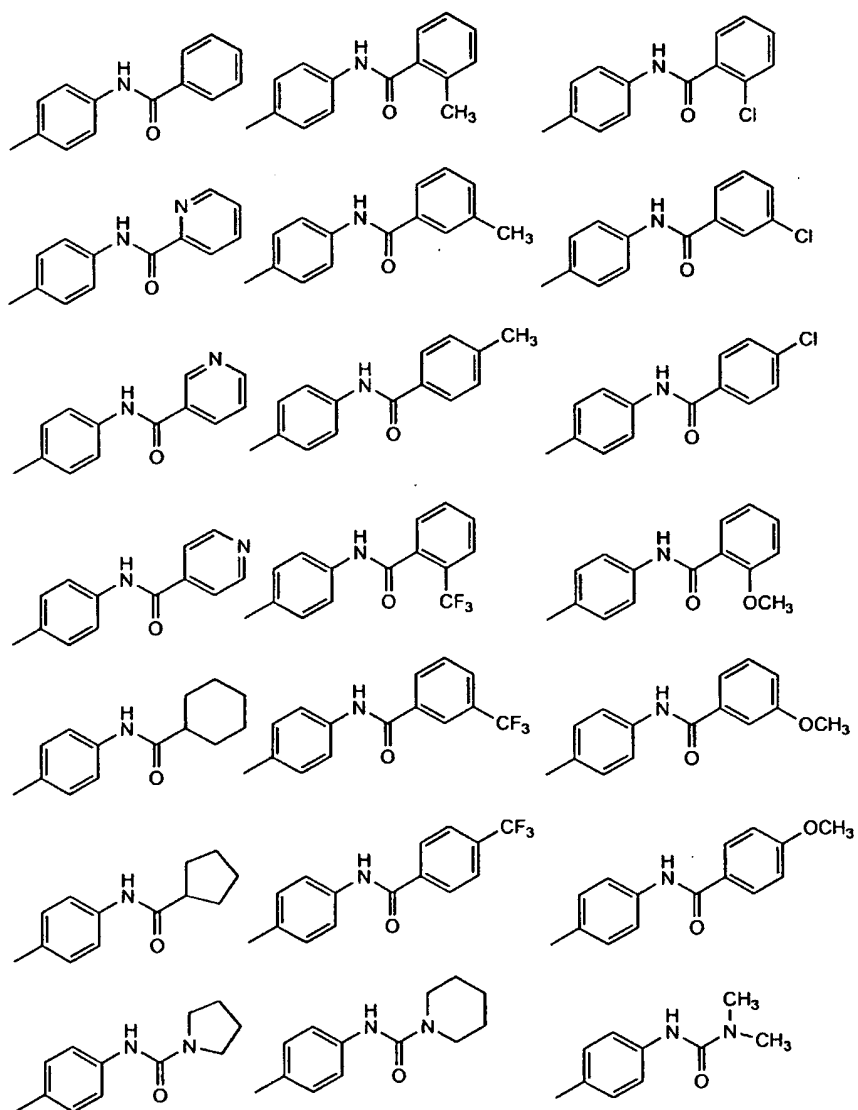
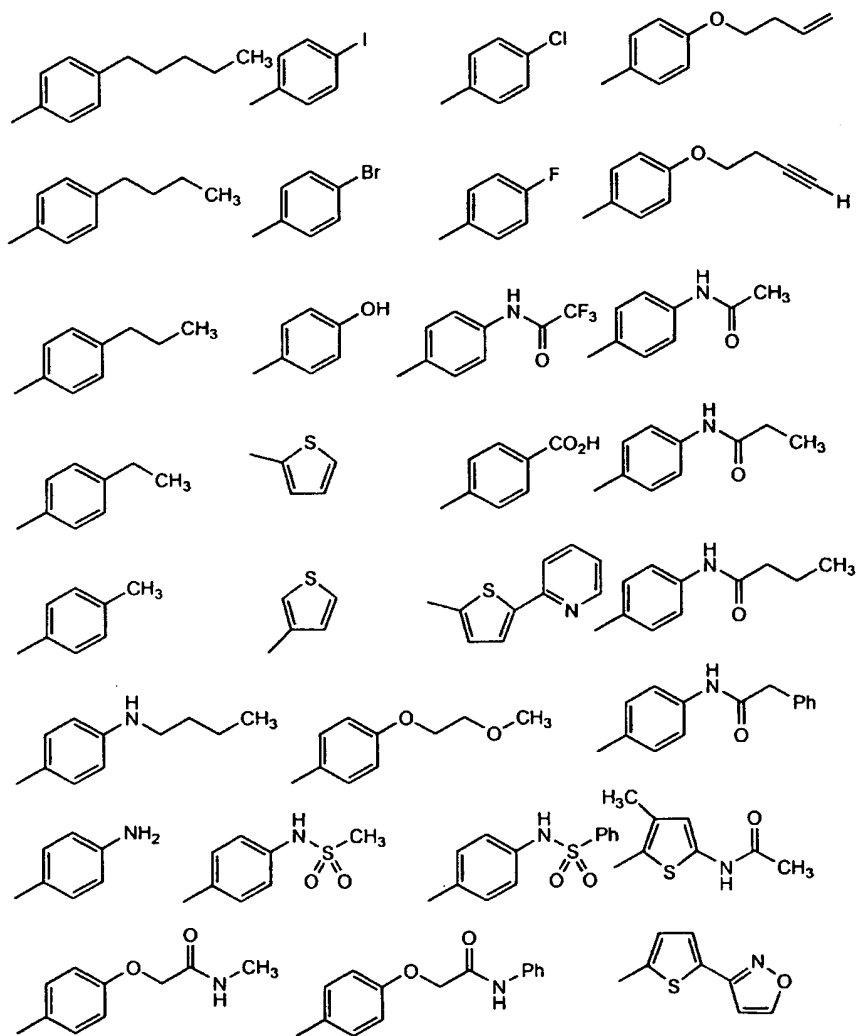
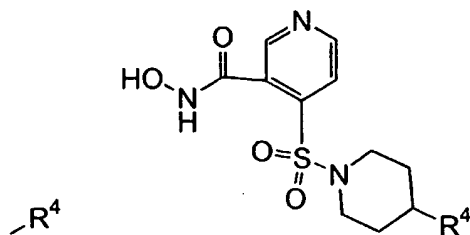
 $\text{R}^4$ 

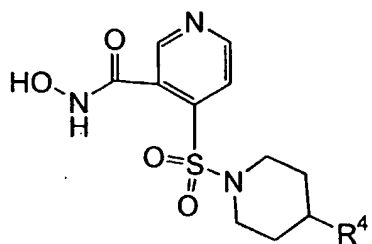
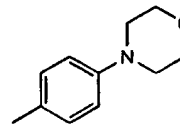
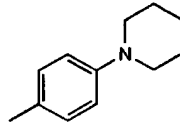
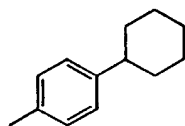
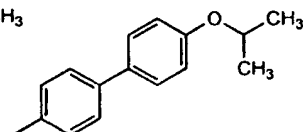
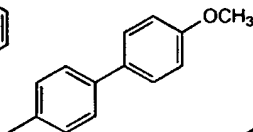
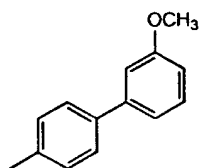
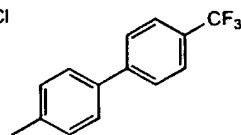
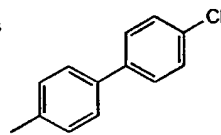
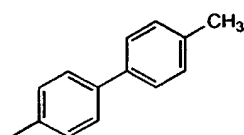
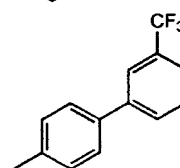
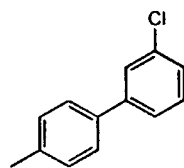
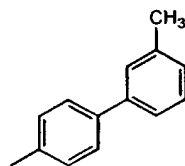
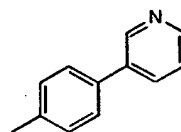
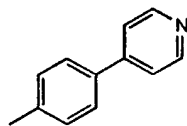
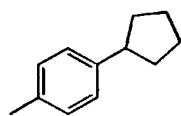
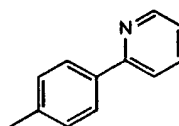
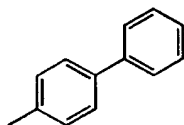
Table 49





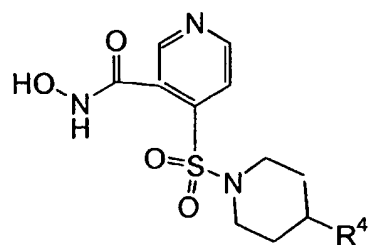
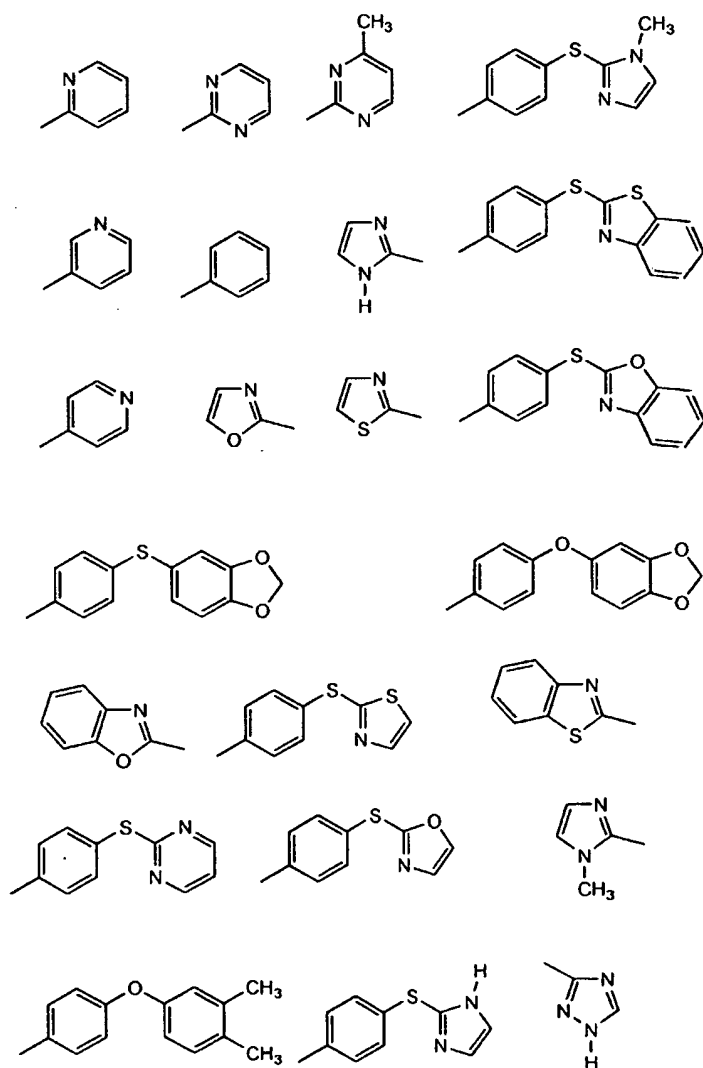
- 131 -

Table 50

 $\text{R}^4$ 

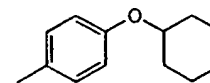
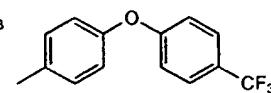
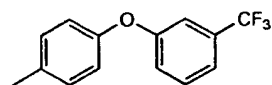
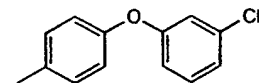
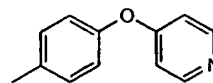
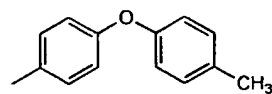
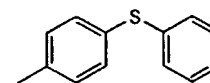
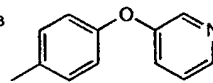
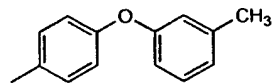
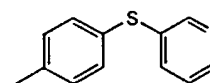
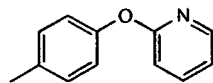
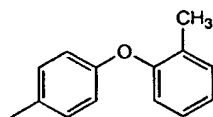
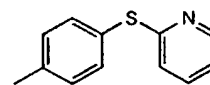
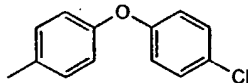
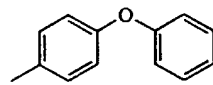
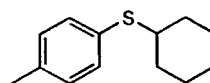
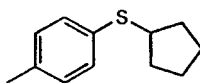
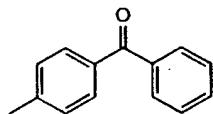
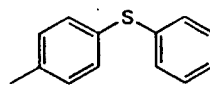
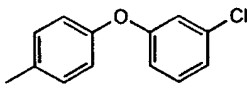
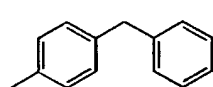
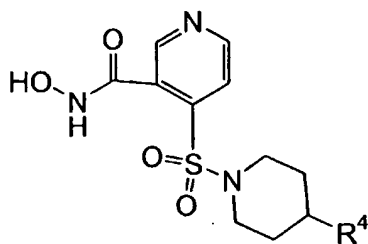
- 132 -

Table 51

 $\text{R}^4$ 

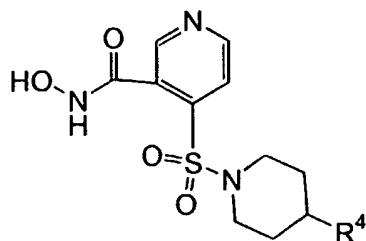
- 133 -

Table 52



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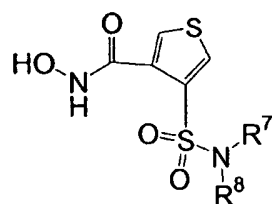
Table 53





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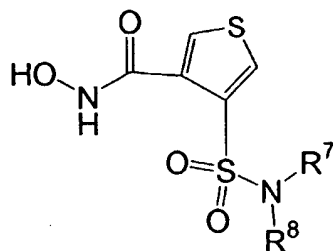
Table 55



Example	-NR <sup>7</sup> R <sup>8</sup>	Example	-NR <sup>7</sup> R <sup>8</sup>
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

-137-

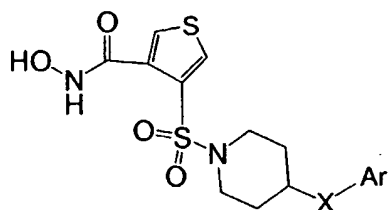
Table 56



Example	$-NR^7R^8$	Example	$-NR^7R^8$
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

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Table 57

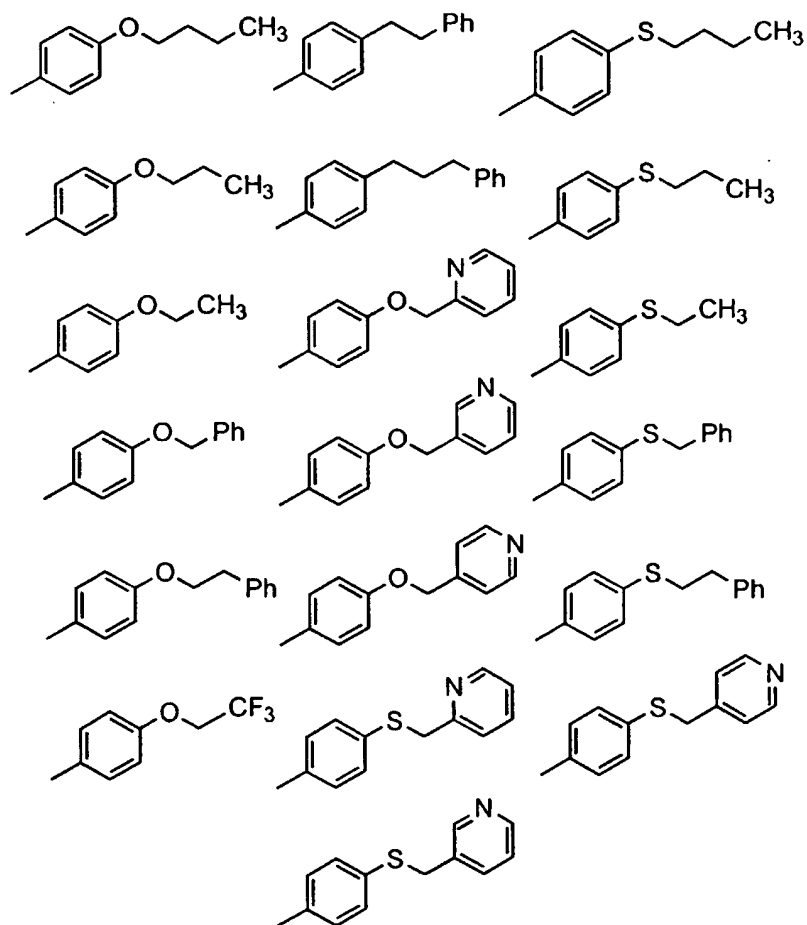
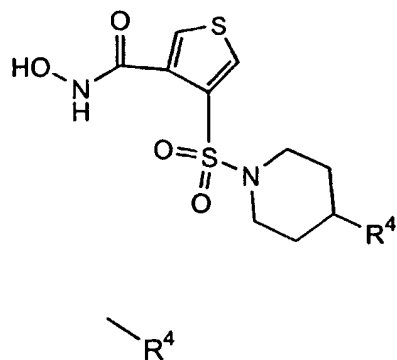


Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	



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Table 58



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Table 59

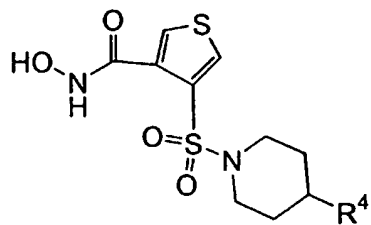
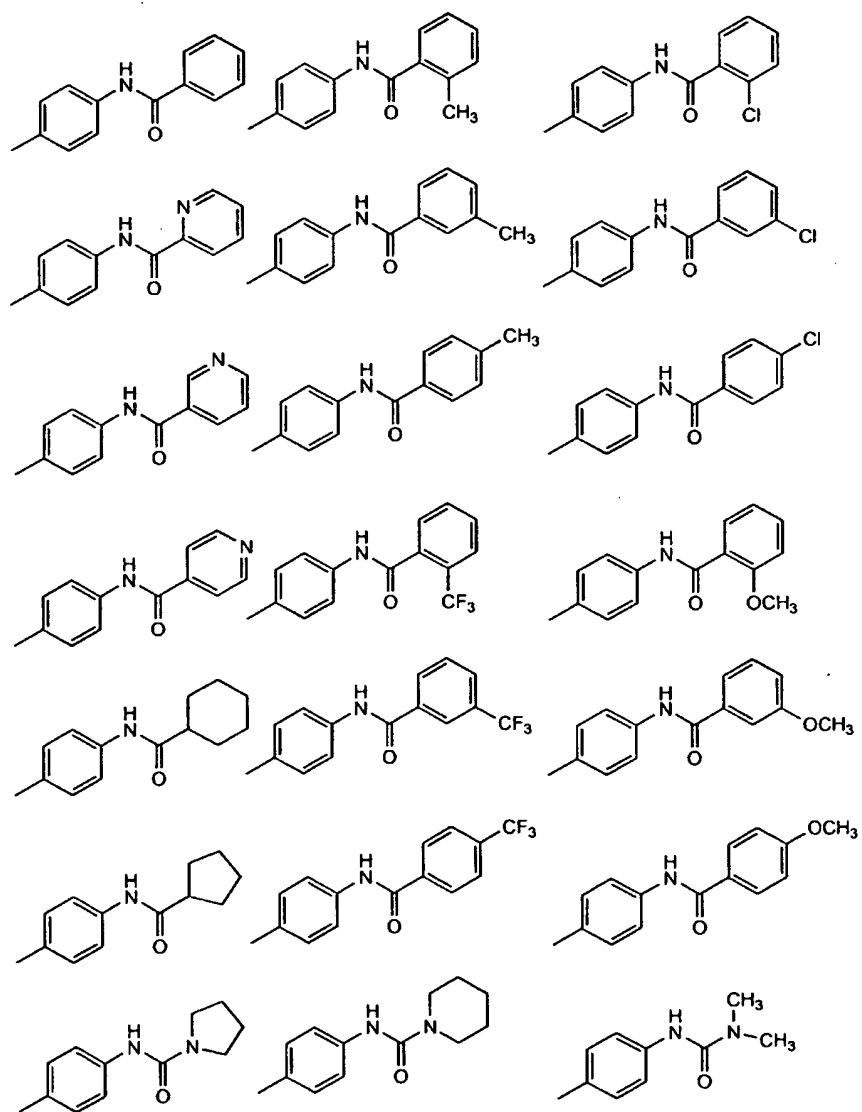
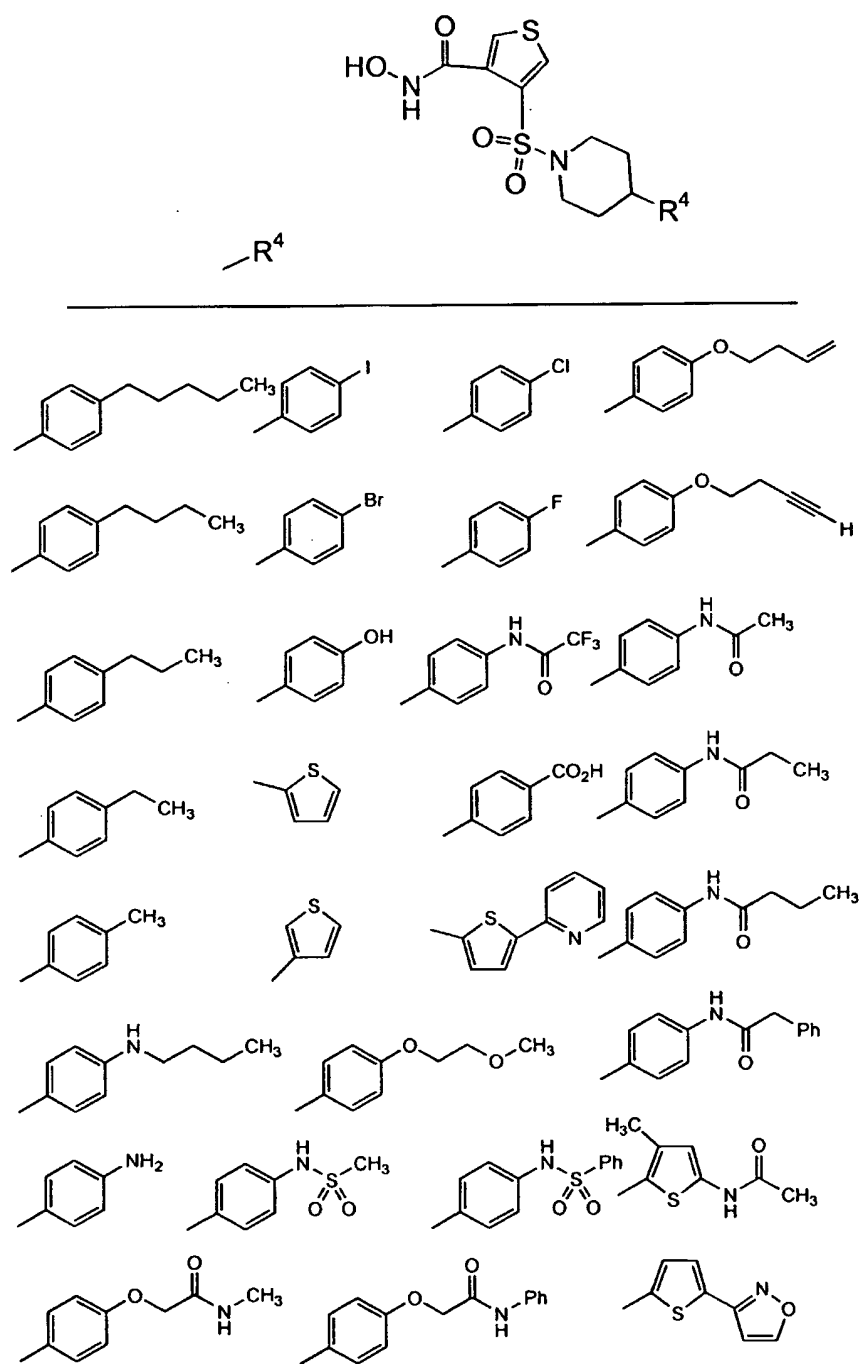
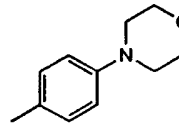
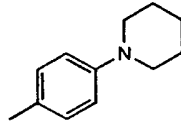
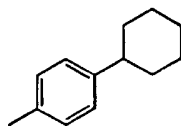
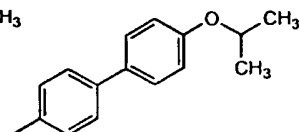
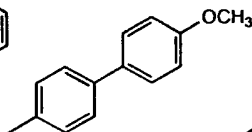
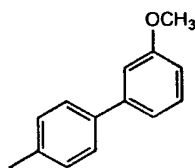
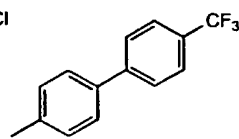
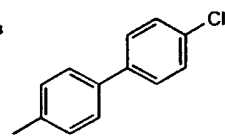
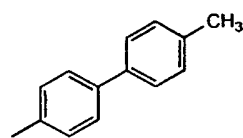
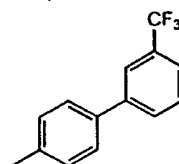
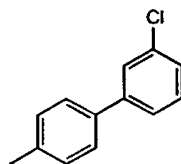
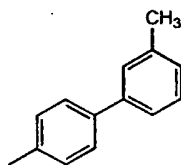
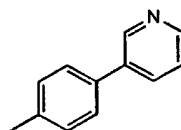
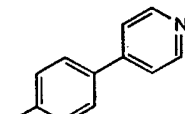
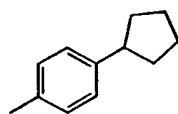
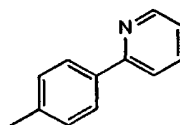
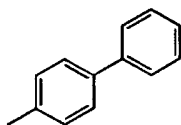
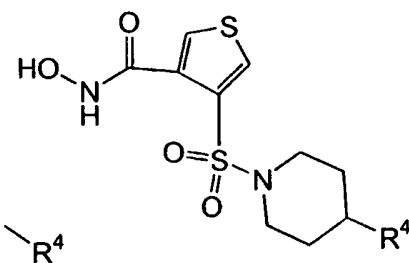
 $\text{R}^4$ 

Table 60



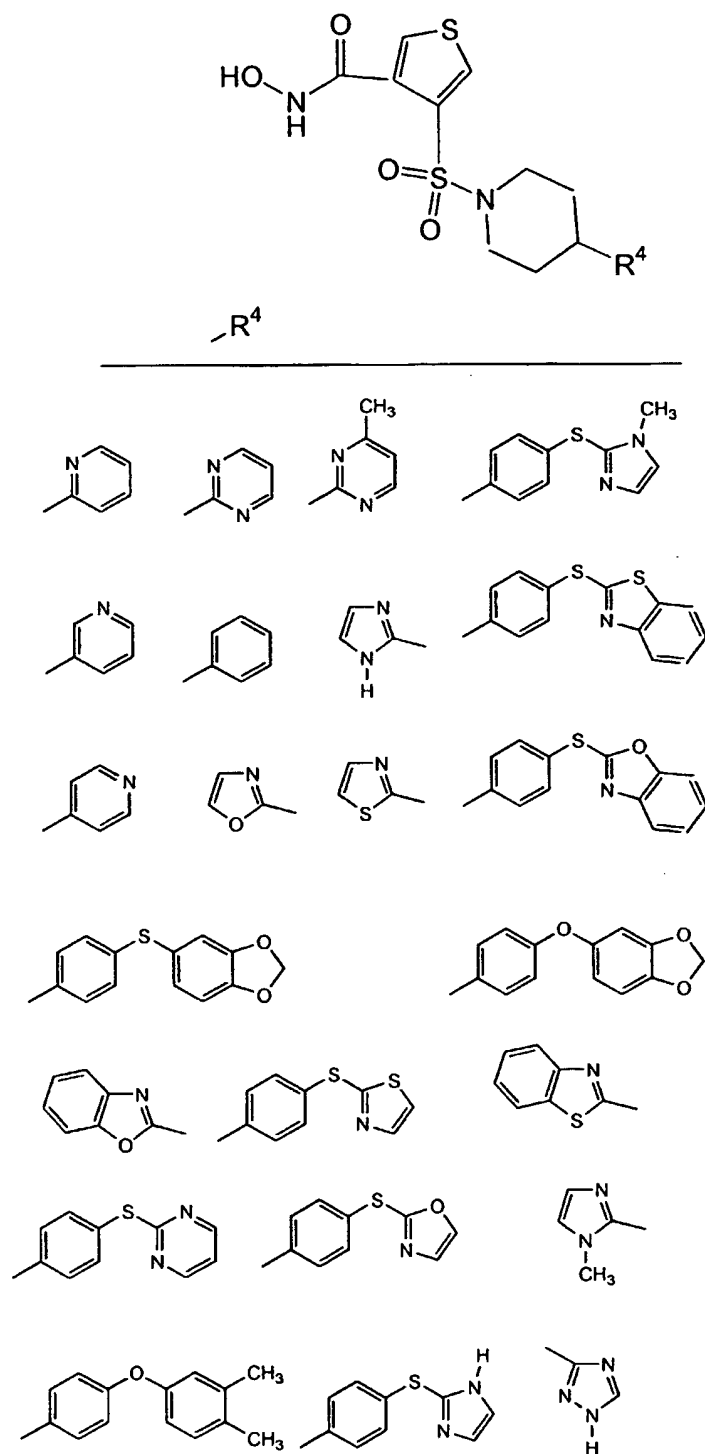
- 142 -

Table 61



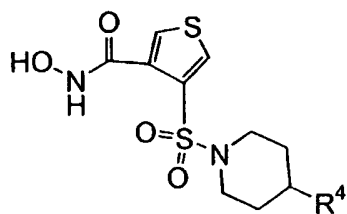
- 143 -

Table 62



- 144 -

Table 63



R<sup>4</sup>

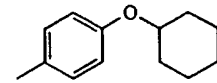
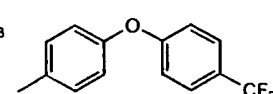
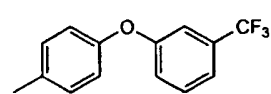
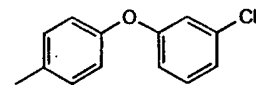
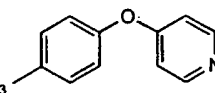
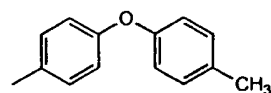
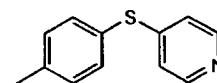
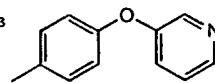
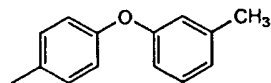
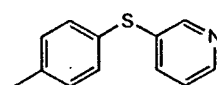
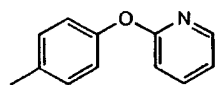
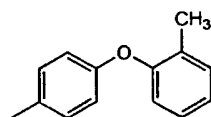
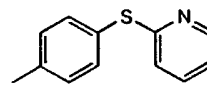
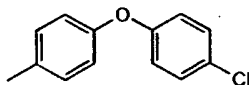
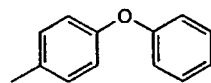
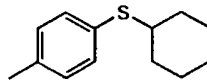
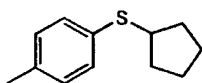
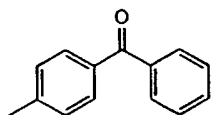
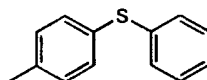
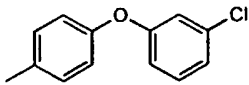
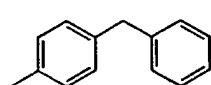


Table 64

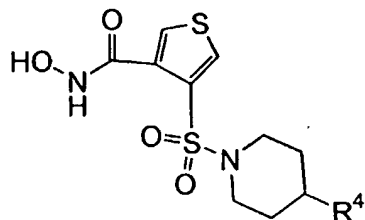
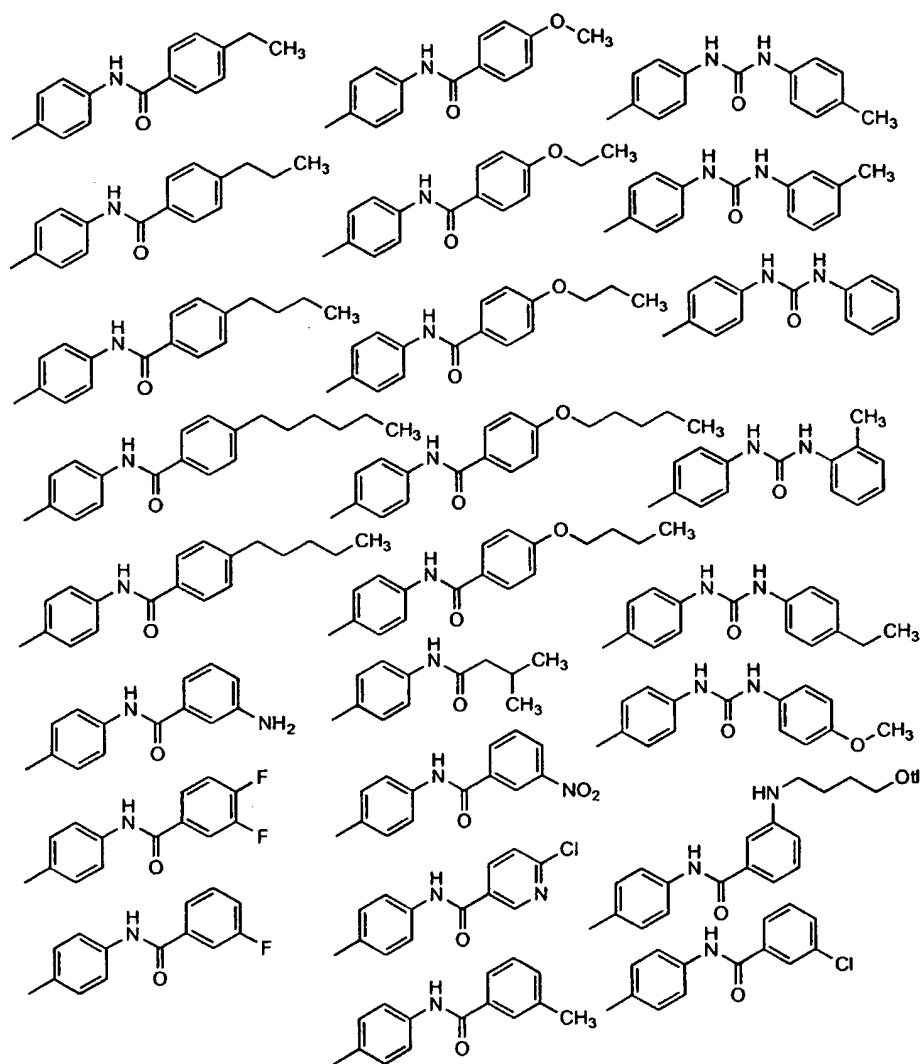
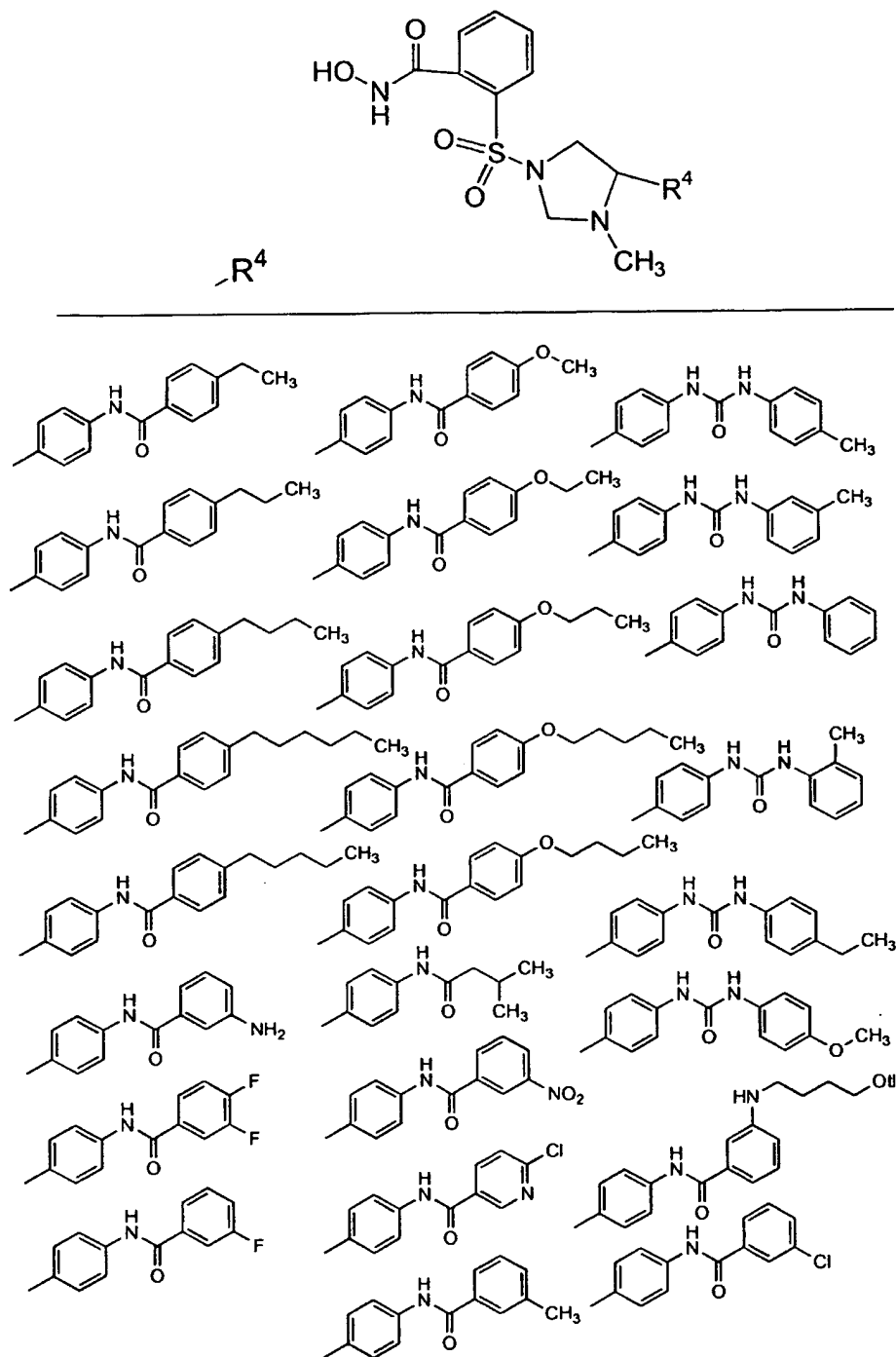
 $\mathbb{R}^4$ 



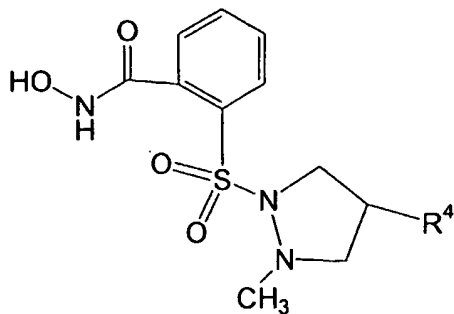


Table 66



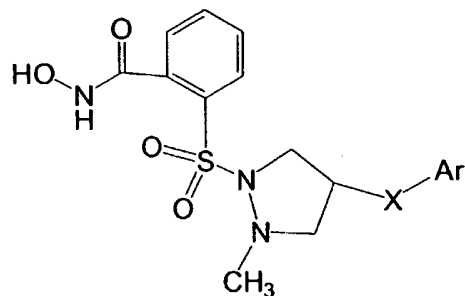
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Table 67



Example	R <sup>4</sup>	Example	R <sup>4</sup>
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

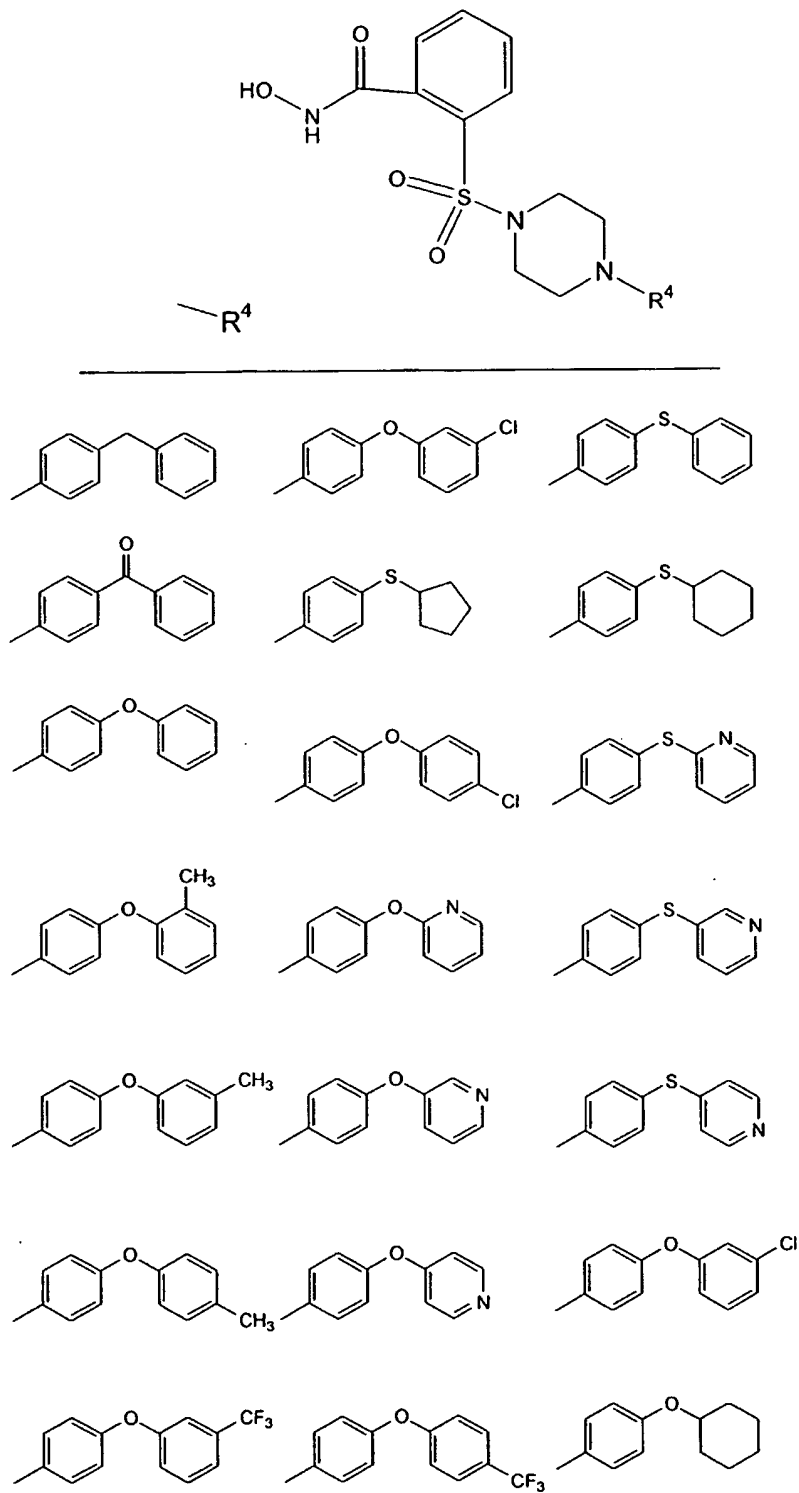
Table 68



Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

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Table 69



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Table 70

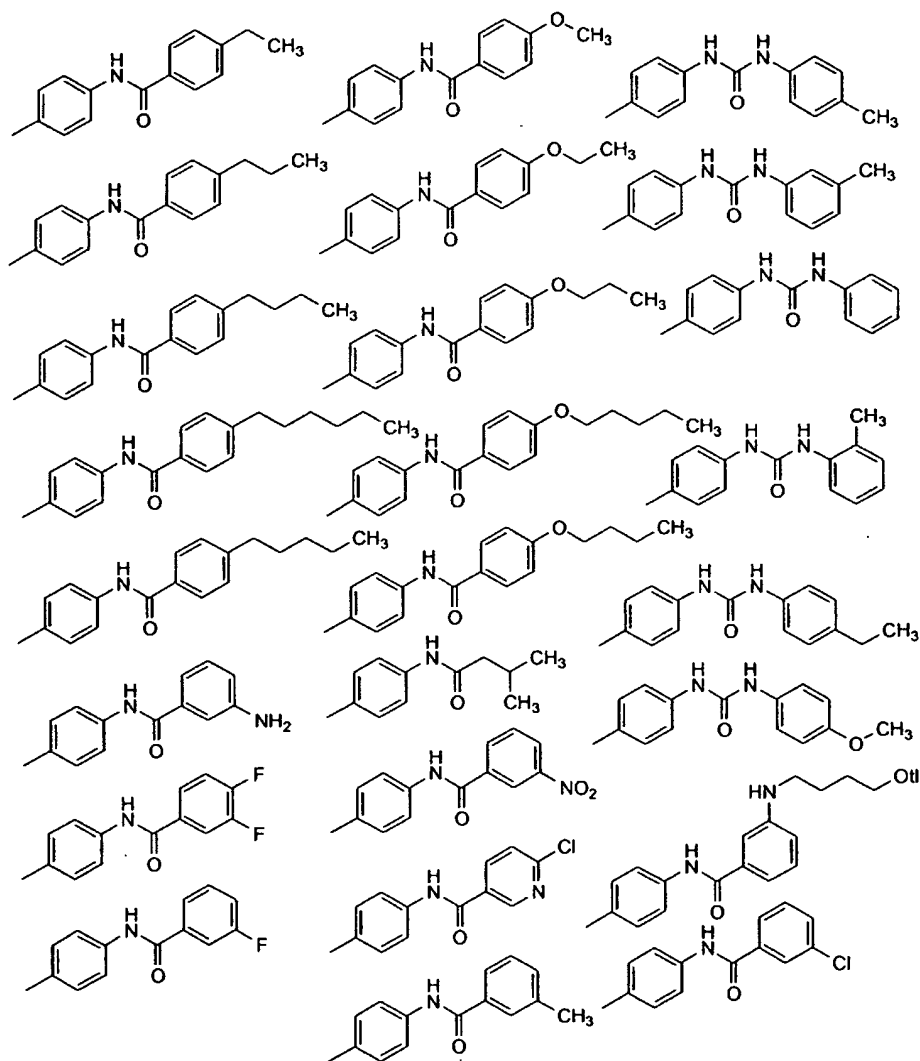
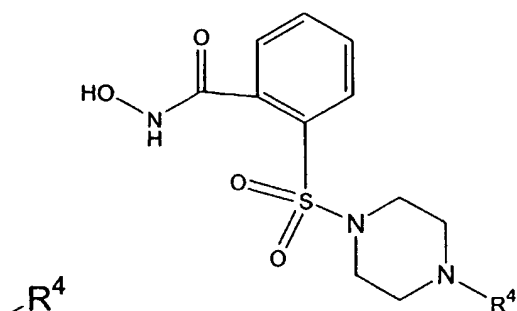


Table 71

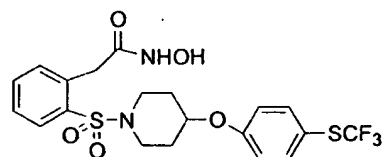
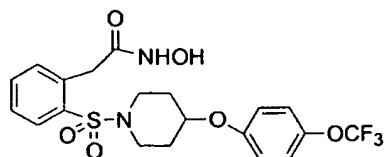
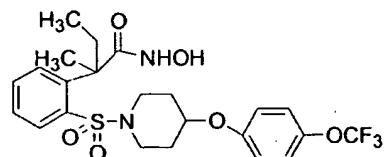
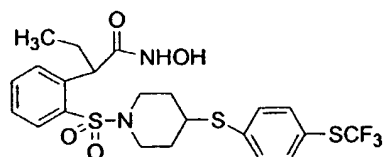
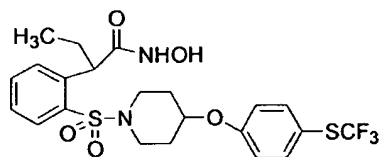
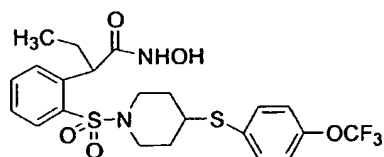
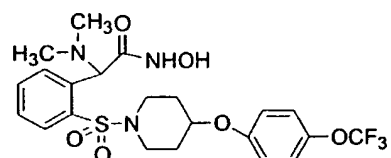
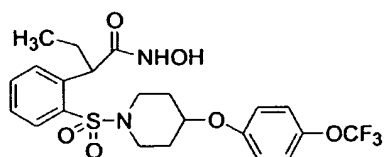
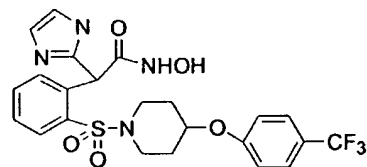
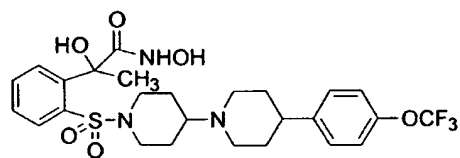
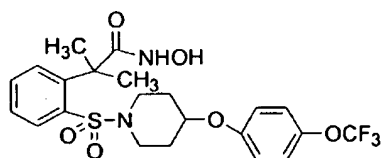
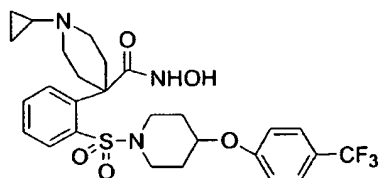
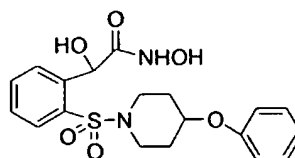


Table 72

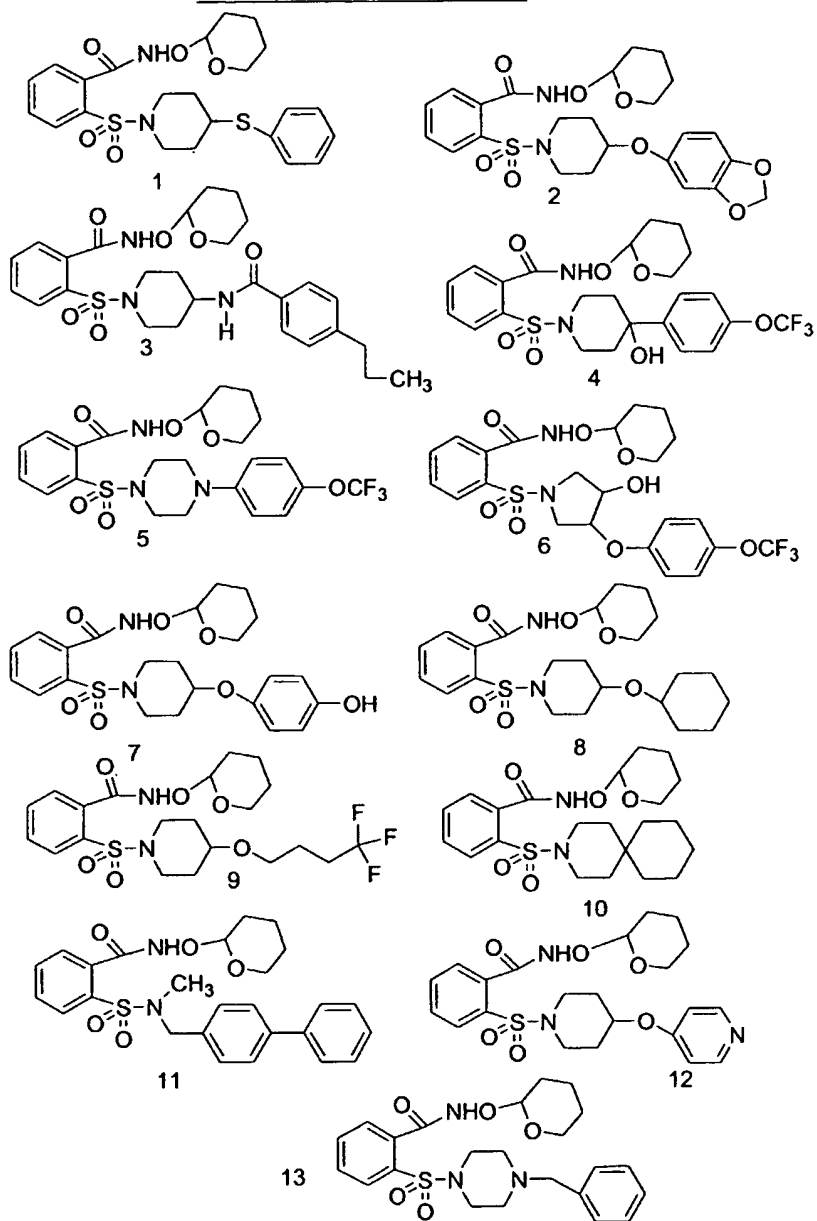


Table 73

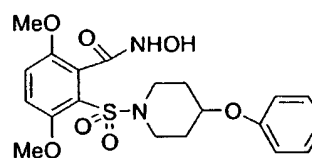
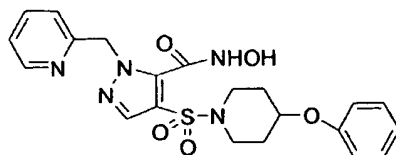
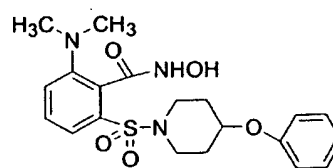
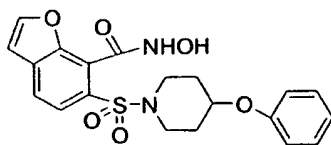
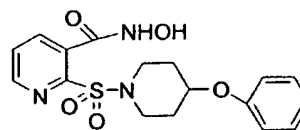
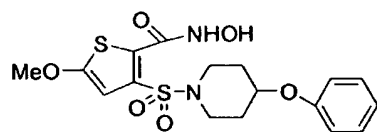
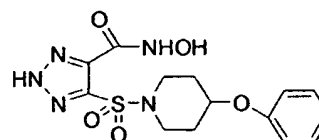
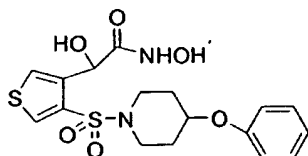
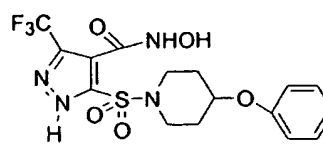
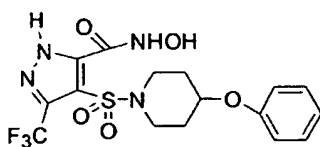
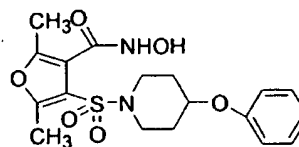
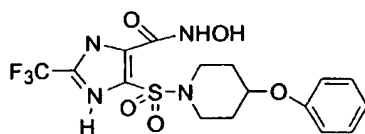




Table 74

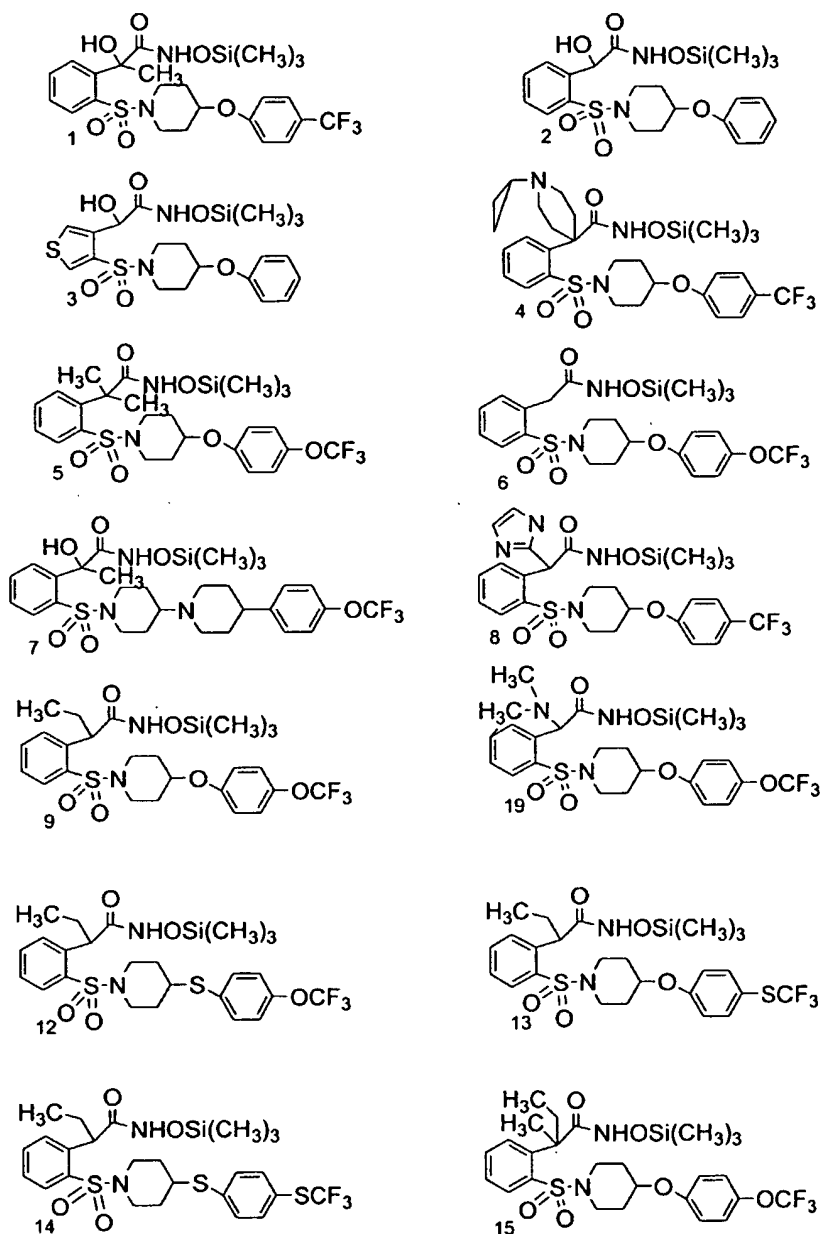
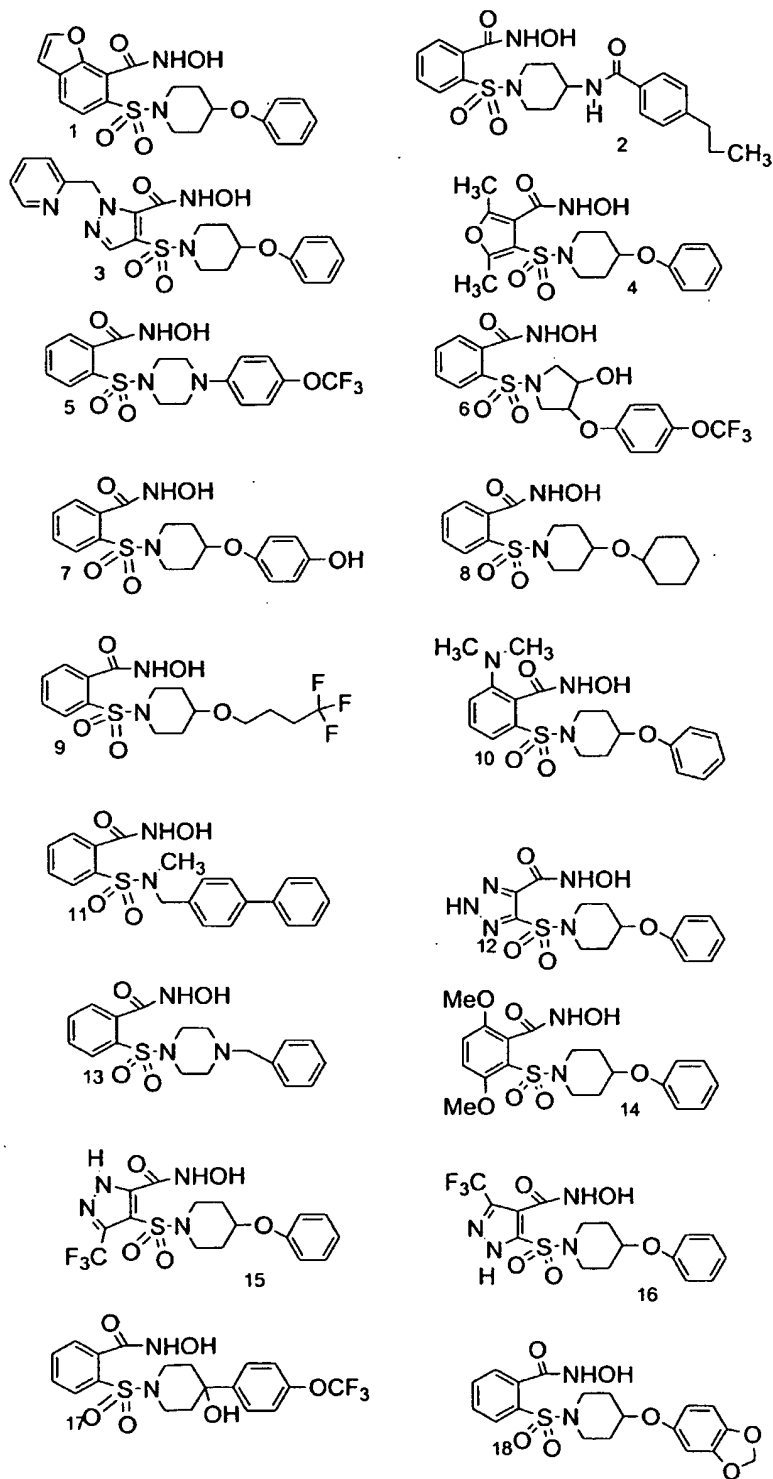


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Table 76

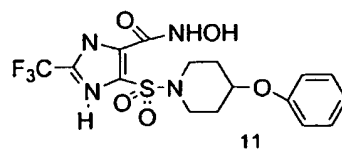
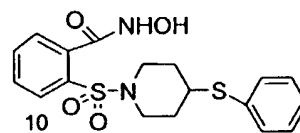
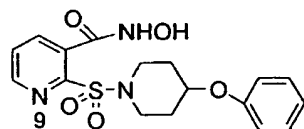
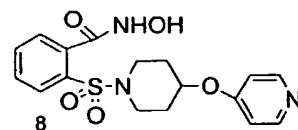
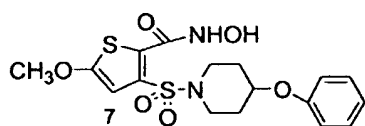
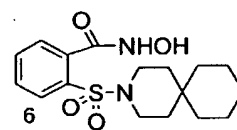
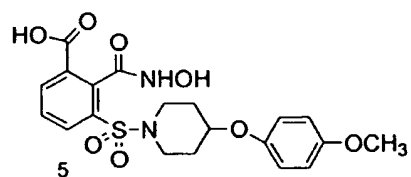
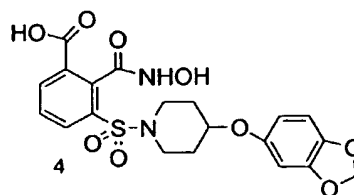
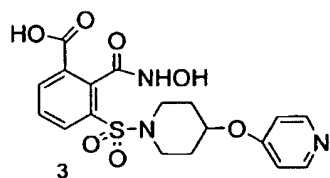
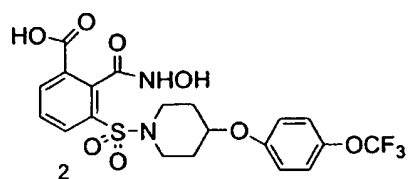
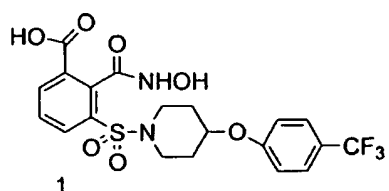
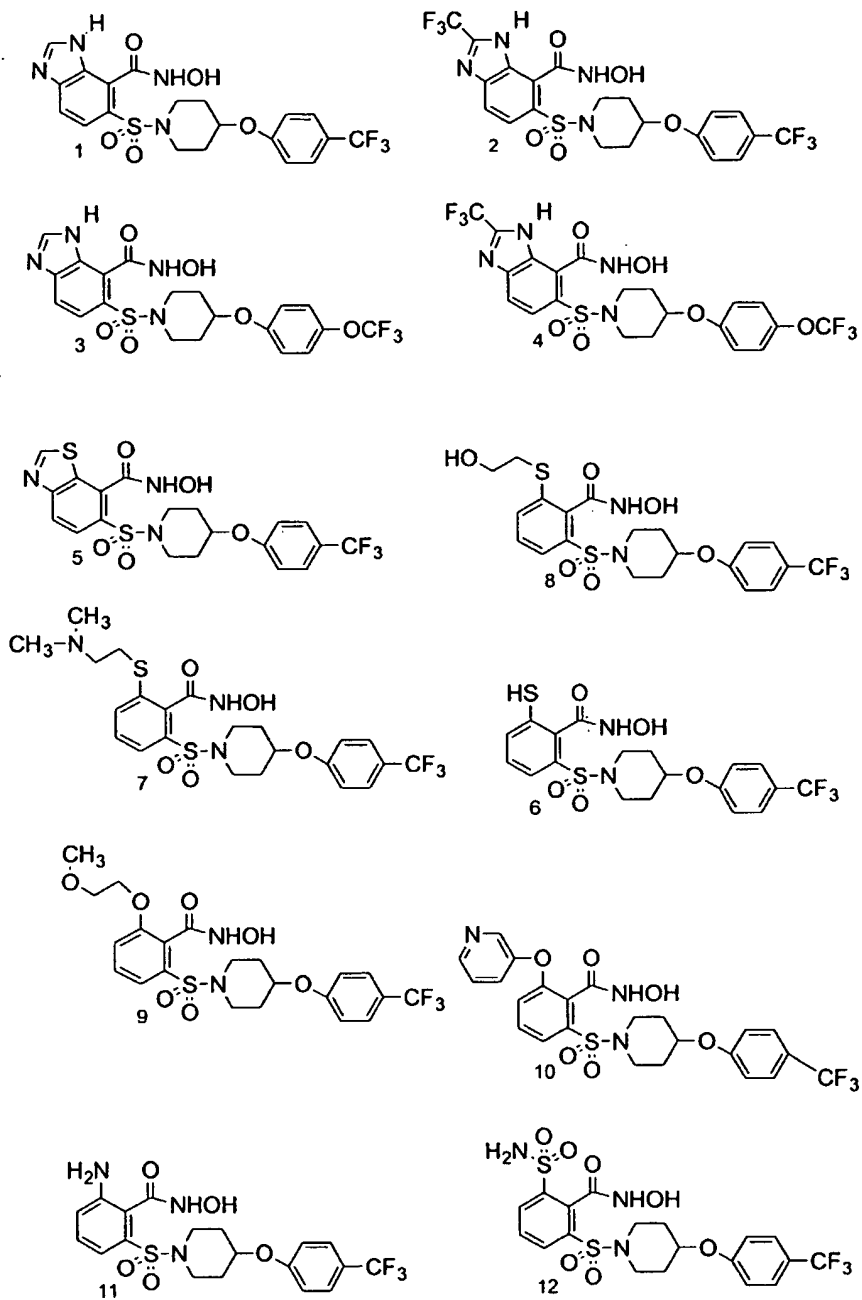


Table 77



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Table 78

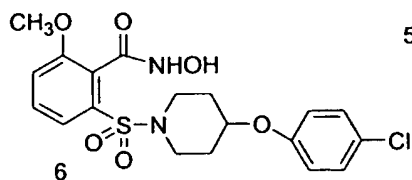
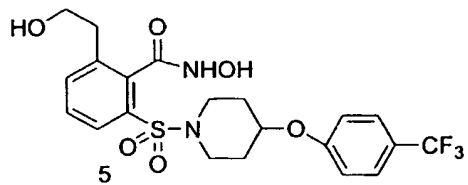
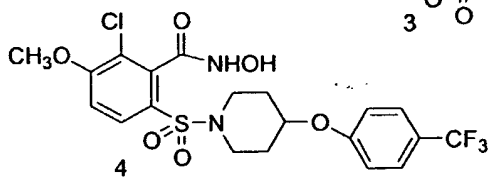
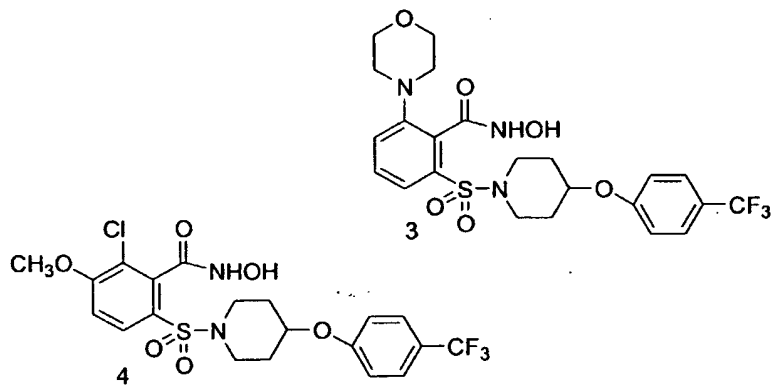
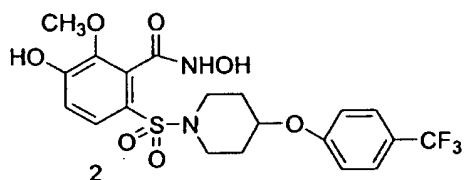
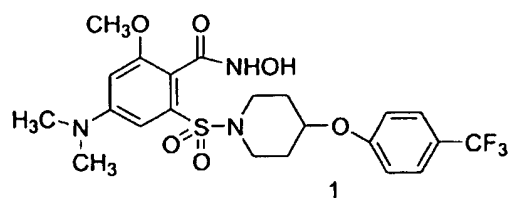


Table 79

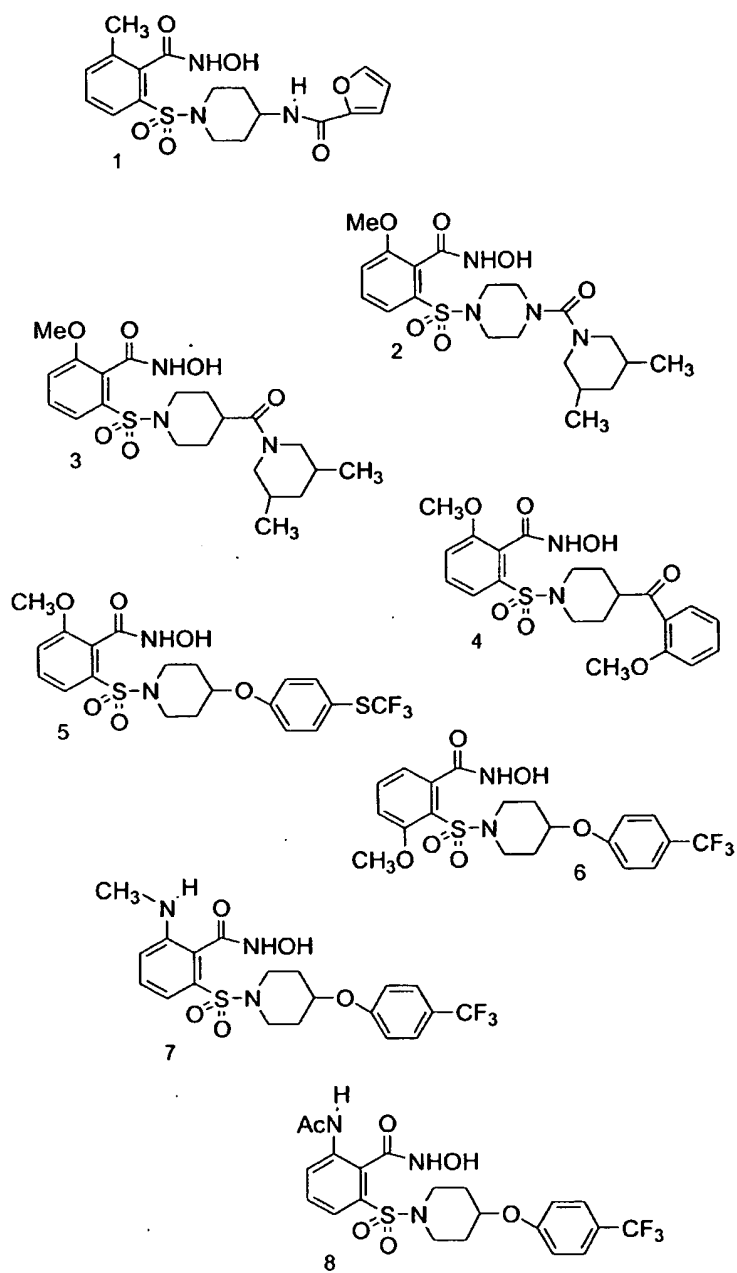
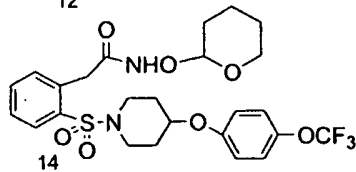
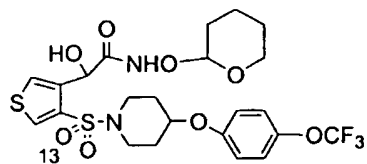
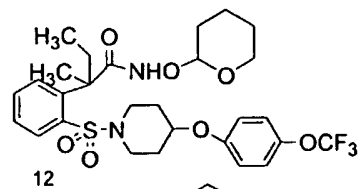
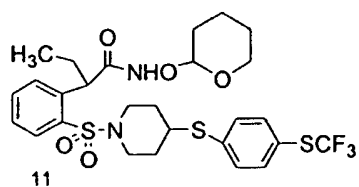
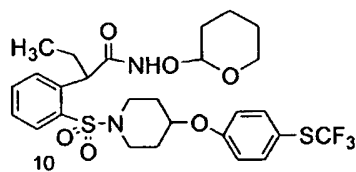
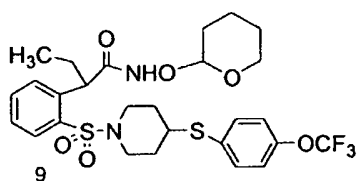
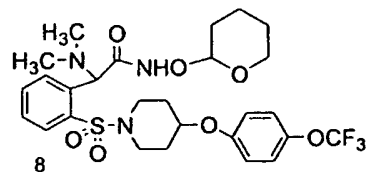
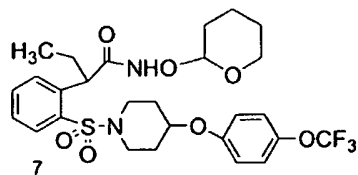
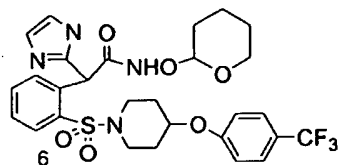
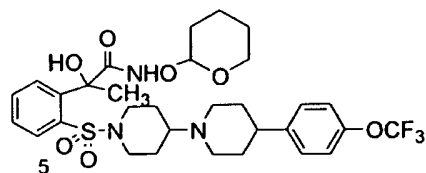
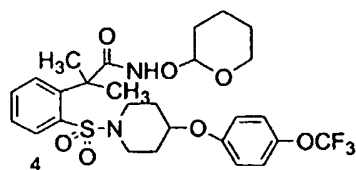
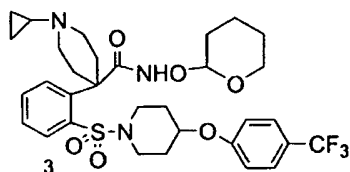
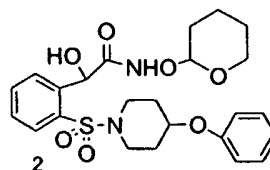
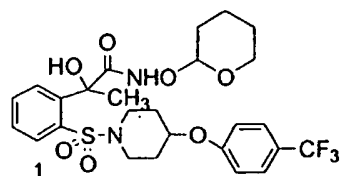
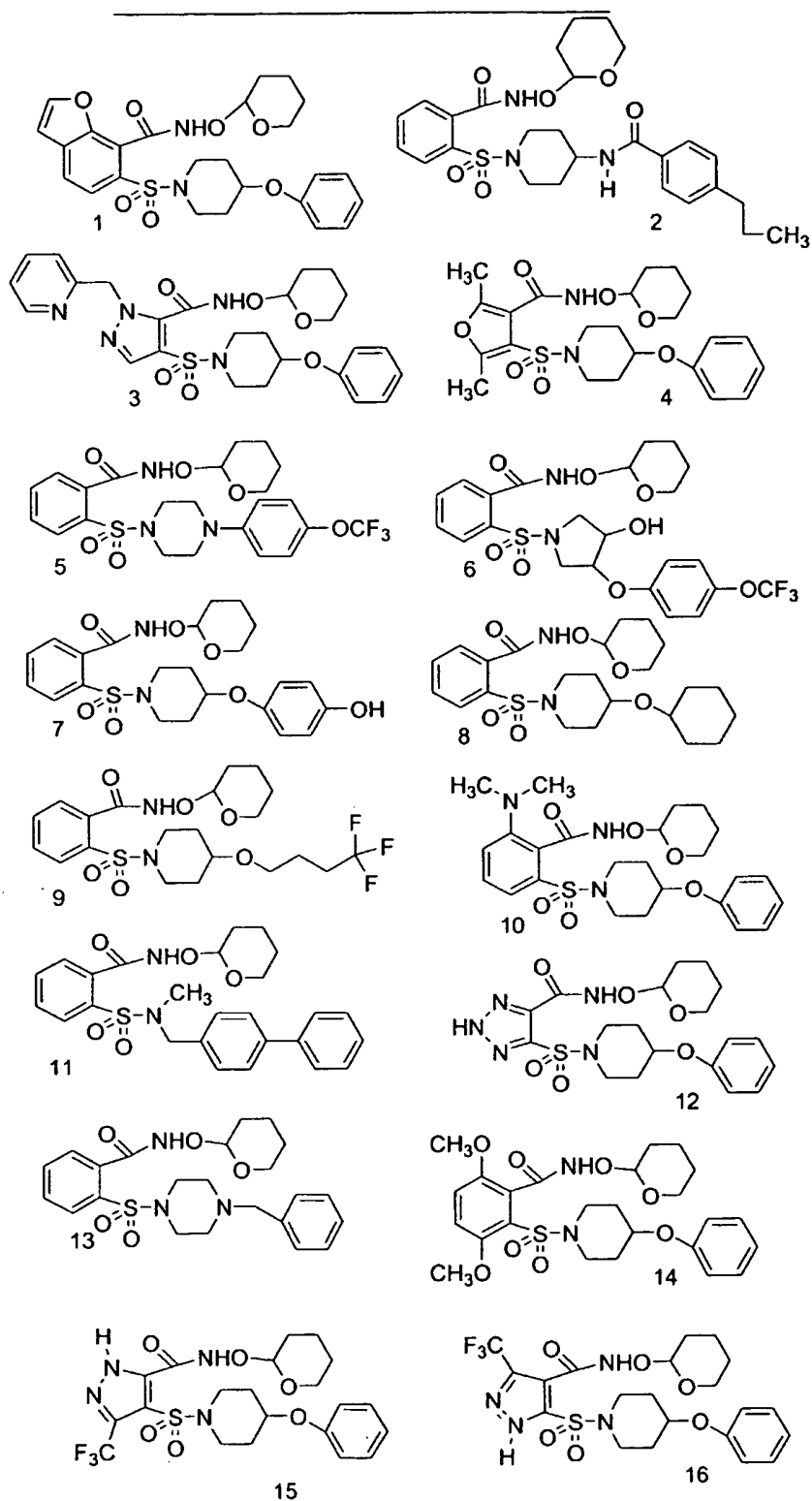


Table 80



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Table 81





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Table 82

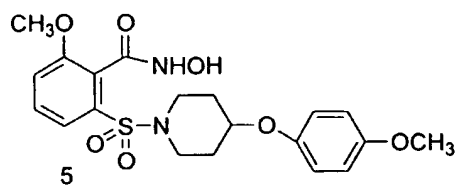
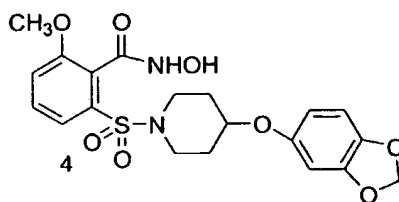
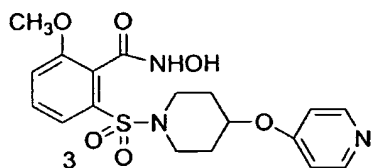
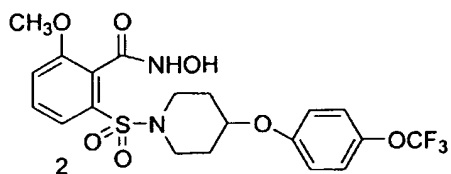
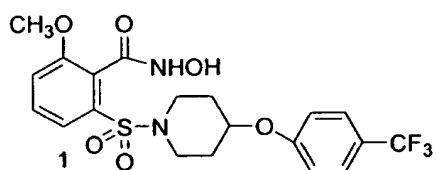


Table 83

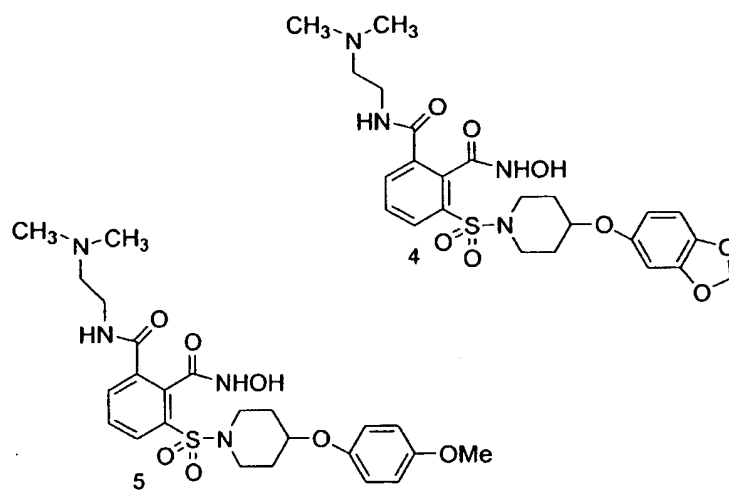
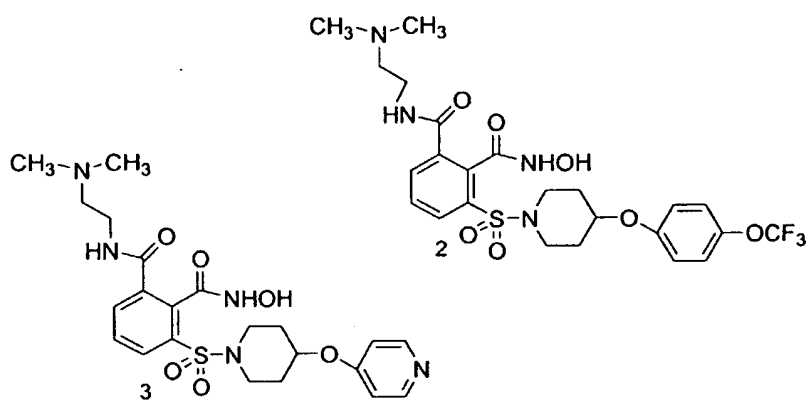
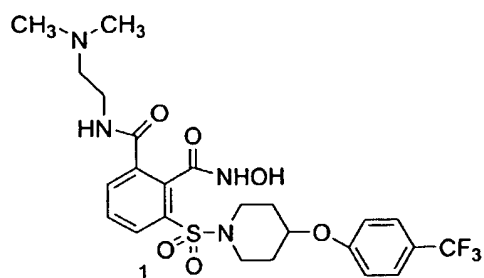
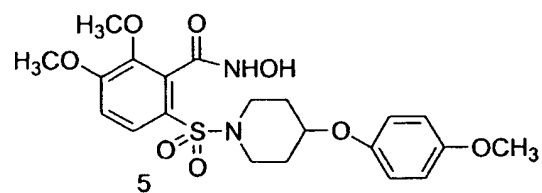
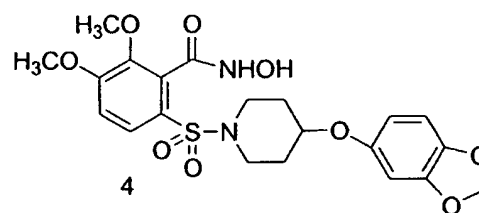
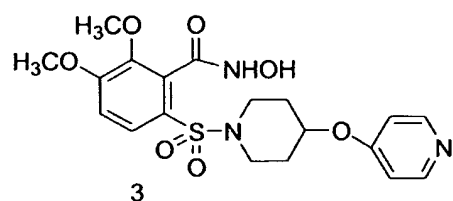
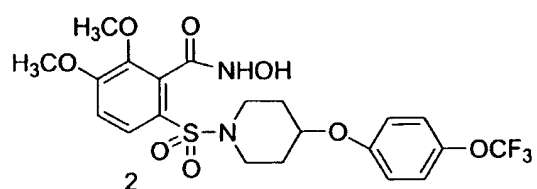
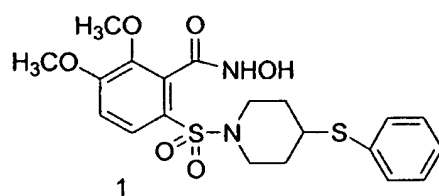
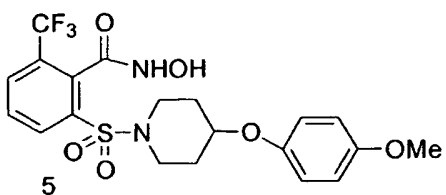
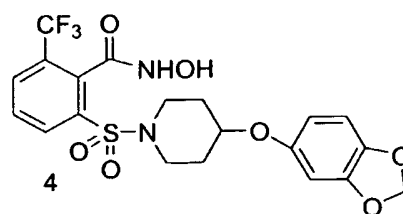
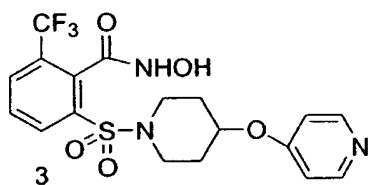
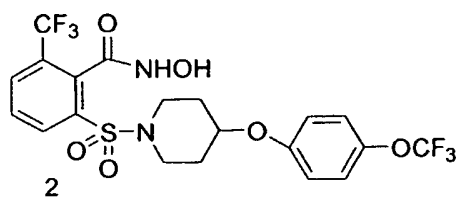
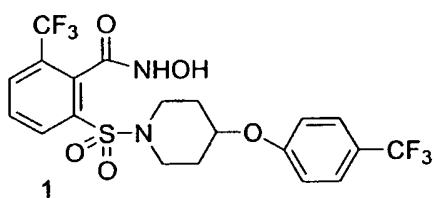


Table 84



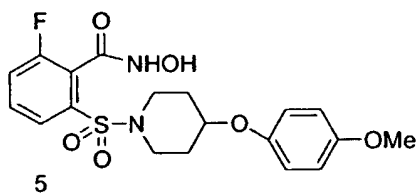
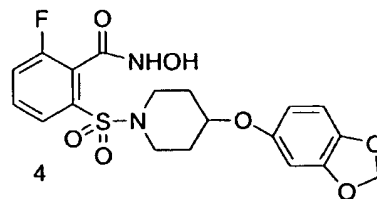
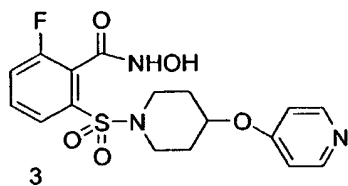
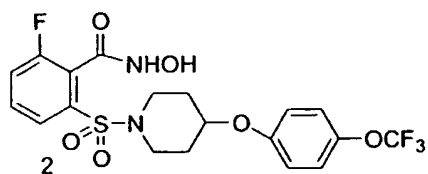
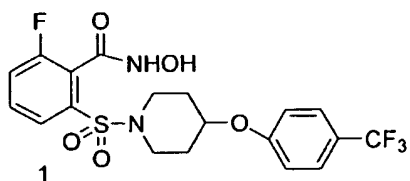
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Table 85



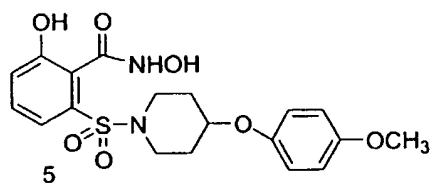
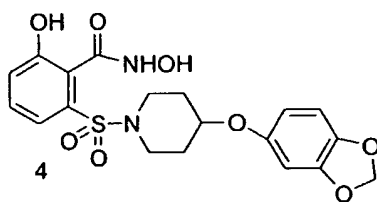
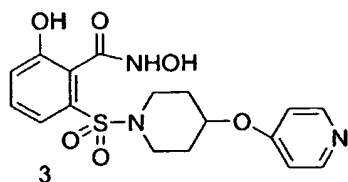
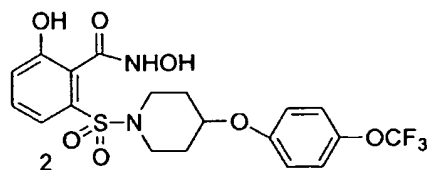
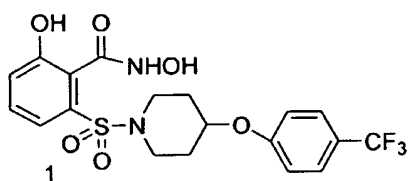
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Table 86



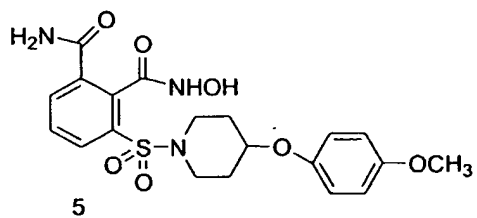
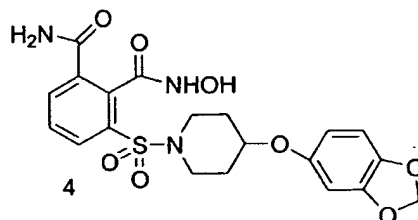
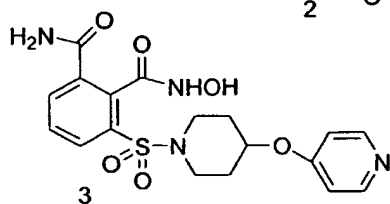
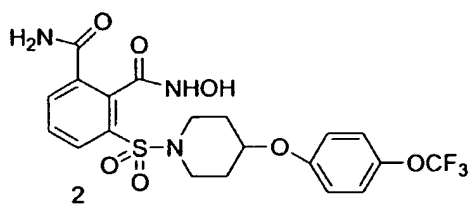
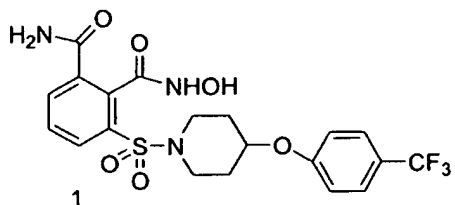
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Table 88



Treatment Process

5 mammal having a condition associated with  
pathological matrix metalloprotease activity is also  
contemplated. That process comprises administering a  
compound described hereinbefore in an MMP enzyme-  
10 inhibiting effective amount to a mammalian host  
having such a condition. The use of administration  
repeated a plurality of times is particularly  
contemplated.

A contemplated compound is used for  
15 treating a host mammal such as a mouse, rat, rabbit,  
dog, horse, primate such as a monkey, chimpanzee or  
human that has a condition associated with  
pathological matrix metalloprotease activity.

Also contemplated is the similar use of a  
20 contemplated compound in the treatment of a disease  
state that can be affected by the activity of  
metalloproteases such as TNF- $\alpha$  convertase. Exemplary  
of such disease states are the acute phase responses  
of shock and sepsis, coagulation responses, hemorrhage  
25 inflammation, anorexia and cachexia.

In treating a disease condition associated  
with pathological matrix metalloproteinase activity,  
a contemplated MMP inhibitor compound can be used,  
30 where appropriate, in the form of an amine salt  
derived from an inorganic or organic acid. Exemplary  
acid salts include but are not limited to the  
following: acetate, adipate, alginate, citrate,  
aspartate, benzoate, benzenesulfonate, bisulfate,



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butyrate, camphorate, camphorsulfonate, digluconate,  
cyclopentanepropionate, dodecylsulfate,  
ethanesulfonate, glucoheptanoate, glycerophosphate,  
hemisulfate, heptanoate, hexanoate, fumarate,  
5 hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-  
ethanesulfonate, lactate, maleate, methanesulfonate,  
nicotinate, 2-naphthalenesulfonate, oxalate,  
palmoate, pectinate, persulfate, 3-phenylpropionate,  
picrate, pivalate, propionate, succinate, tartrate,  
10 thiocyanate, tosylate, mesylate and undecanoate.

Also, a basic nitrogen-containing group can  
be quaternized with such agents as lower alkyl ( $C_1$ -  
 $C_6$ ) halides, such as methyl, ethyl, propyl, and butyl  
chloride, bromides, and iodides; dialkyl sulfates  
15 like dimethyl, diethyl, dibutyl, and diamyl sulfates,  
long chain ( $C_8$ - $C_{20}$ ) halides such as decyl, lauryl,  
myristyl and dodecyl chlorides, bromides and iodides,  
aralkyl halides like benzyl and phenethyl bromides,  
and others to provide enhanced water-solubility.  
20 Water or oil-soluble or dispersible products are  
thereby obtained as desired. The salts are formed by  
combining the basic compounds with the desired acid.

Other compounds useful in this invention  
that are acids can also form salts. Examples include  
25 salts with alkali metals or alkaline earth metals,  
such as sodium, potassium, calcium or magnesium or  
with organic bases or basic quaternary ammonium  
salts.

In some cases, the salts can also be used  
30 as an aid in the isolation, purification or  
resolution of the compounds of this invention.

Total daily dose administered to a host  
mammal in single or divided doses of an MMP enzyme-

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inhibiting effective amount can be in amounts, for example, of about 0.001 to about 100 mg/kg body weight daily, preferably about 0.001 to about 30 mg/kg body weight daily and more usually about 0.01 to about 10 mg. Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. A suitable dose can be administered, in multiple sub-doses per day. Multiple doses per day can also increase the total daily dose, should such dosing be desired by the person prescribing the drug.

The dosage regimen for treating a disease condition with a compound and/or composition of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as Part of a drug combination. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the preferred dosage regimen set forth above.

A compound useful in the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal

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patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975 and Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa

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butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and  
5 release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or  
10 more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium  
15 stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or  
20 tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium  
25 citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of  
30 aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or

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diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

#### Preparation of Useful Compounds

Procedures are provided in the discussion and schemes that follow of exemplary chemical transformations that can be useful for the preparation of compounds of this invention. These syntheses, as with all of the reactions discussed herein, can be carried out under a dry inert atmosphere such as a nitrogen or argon if desired. Selected reactions known to those skilled in the art, can be carried out under a dry atmosphere such as dry air whereas other synthetic steps, for example,

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aqueous acid or base ester or amide hydrolyses, can be carried out under laboratory air.

Aryl and heteroaryl aryl compounds of this invention as define above by W can be prepared in a similar manner as is known to those skilled in the art. It should be understood that the discussion below refers to both aromatic systems, i. e., heteroaromatics and carbon aromatics, even though only one may be specifically mentioned.

In general, the choices of starting material and reaction conditions can vary as is well know to those skilled in the art. Usually, no single set of conditions is limiting because variations can be applied as required and selected by one skilled in the art. Conditions will also will be selected as desired to suit a specific purpose such as small scale preparations or large scale preparations. In either case, the use of less safe or less environmentally sound materials or reagents will usually be minimized. Examples of such less desirable materials are diazomethane, diethyl ether, heavy metal salts, dimethyl sulfide, some halogenated solvents, benzene and the like. In addition, many starting materials can be obtained from commercial sources from catalogs or through other arrangements.

An aromatic compound of this invention where y is 1 can be prepared as illustrated by converting a carbonyl group bonded to an aromatic (e.g., benzene) ring ortho-substituted with a sulfide. The sulfide can be prepared via a nucleophilic displacement reaction of the ortho fluoride.

The nucleophile can be a thiol or thiolate anion prepared from a aryl thiol discussed below. A

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preferred thiol is 4-phenoxybenzenethiol converted in situ into its anion (thiolate) using potassium carbonate in iso-propyl alcohol at reflux temperature.

5           The carbonyl group can be a aldehyde, ketone or carboxylic acid derivative, i.e, a protected carboxylic acid or hydroxamate. A preferred carbonyl group is an aldehyde and a preferred aldehyde is 2-fluorobenzaldehyde (ortho-  
10 fluorobenzaldehyde). A ketone can be converted by oxidation into an acid and/or an acid derivative using reagents such as those discussed below for oxidation of a sulfide or other methods well known in the art. It is noted that this oxidation can  
15 accomplish the oxidation of a sulfide intermediate into the corresponding sulfone in the same reaction system; i.e., in the same pot, if desired.

          The carbonyl group can then be homologated if desired by reaction with an anion to form an  
20 addition compound. An example of a homologation reagent is a tri-substituted methane compound such as tetraethyl dimethylammoniummethylenediphosphonate or trimethylorthoformate. Tetraethyl dimethylammonium-methylenediphosphonate is preferred. Hydrolysis of  
25 the reaction product can provide a phenylacetic substituted on the aromatic ring with a sulfide of this invention. Acid hydrolysis is preferred. Acids and bases are discussed below and hydrochloric acid is preferred.

30           The sulfide can then be oxidized to form a sulfone in one or two steps as discussed below. A preferred oxidizing agent is hydrogen peroxide in acetic acid. The carboxylic acid product or

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intermediate of this invention can then be converted into a protected derivative such as an ester or converted into an activated carboxyl group for reaction with hydroxylamine or and protected  
5 hydroxylamine; i.e, a hydroxamate. The conversion of an acid into a hydroxamate is discussed below as is the coupling process and removal of a protecting group if required.

The preferred protected hydroxamic acid  
10 derivative is the O-tetrahydropyranyl compound and the preferred coupling procedure utilizes a diimide (EDC), hydroxybenzotriazol and DMF solvent for the coupling reaction to form the intermediate hydroxybenzotriazol activated ester. A preferred  
15 reagent for removal of the THP protecting group is hydrochloric acid.

Alkylation of the acid at the carbon alpha to the carbonyl group to form the compounds of this invention can be carried out by first forming an  
20 anion using a base. Bases are discussed below. The preferred bases are strong bases that are either hindered and/or non-nucleophilic such as lithium amides, metal hydrides or lithium alkyls.

Following or during formation of the anion,  
25 an alkylating agent (an electrophile) is added that undergoes a nucleophilic substitution reaction. Non-limiting examples of such alkylating agents are haloalkanes, dihaloalkanes, haloalkanes also substituted by an activated ester group or activated  
30 esters and alkanes substituted with sulfate esters.

Activated ester groups are well known in the art and can include, for example, an activated ester of an alcohol or a halo compound, an ester of a



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haloalcohol such as a bromo-, iodo- or chloro-  
derivative of a tosylate, triflate or mesylate  
activated ester. Compounds wherein, for example, R<sup>2</sup>  
and R<sup>3</sup> are taken together as defined above, can be  
5 prepared using disubstituted alkylating agent; i.e.,  
alkylating agents with two leaving groups in the same  
molecule. For example, 1,5-dihalo-diethylether or  
analogous reagents containing one or more sulfate  
ester leaving groups replacing one or more halogens  
10 can be used to form a pyran ring. A similar sulfur,  
nitrogen or protected nitrogen alkylating agent can  
be used to form a thiapyran or piperidine ring. A  
thiapyran can be oxidized to form a sulfoxide or a  
sulfone using methods discussed herein. A leaving  
15 group in an electrophilic reagent, as is well known  
in the art, can be a halogen such as chlorine,  
bromine or iodine or an active ester such as a  
sulfonate ester, e.g., toluenesulfonate (tosylate),  
triflate, mesylate and the like as discussed above.

20           The conversion of a cyclic amino acid,  
heterocycle or alpha-amino acid defined by R<sup>2</sup> and R<sup>3</sup>  
that can include an amino acid (nitrogen  
heterocycle), which can be protected or unprotected,  
into a compound of this invention can be accomplished  
25 by alkylation or acylation. The carboxylic acid  
group can be protected with a group such as an alkyl  
ester such as methyl, ethyl, tert-butyl and the like  
or a tetrahydropyranyl ester or an arylalkyl ester  
such as benzyl or it can remain as a carboxylic acid.  
30 A protected amino acid such as an ethyl ester is  
preferred. The substituent on the heterocycle group  
is as defined above and can include hydrogen, tert-  
butoxycarbonyl (BOC or tBOC), benzyloxycarbonyl (Z)

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and iso-butyloxycarbonyl groups. In addition, the amine can be considered as being a protected intermediate as well as being a product of this invention when the N-substituent is not hydrogen.

5           The nitrogen substituent on the amino acid portion of the compounds of this invention can be varied. In addition, that variation can be accomplished at different stages in the synthetic sequence based on the needs and objectives of the skilled person preparing the compounds of this invention. The nitrogen side chain variations can include replacing the hydrogen substituent with a alkyl, arylalkyl, alkene or alkyne.

10           This can be accomplished by methods well known in the art such as alkylation of the amine with an electrophile such as halo- or sulfate ester (activated ester) derivative of the desired sidechain. An alkylation reaction is typically carried out in the presence of a base such as those discussed above and in a pure or mixed solvent as discussed above. A preferred base is potassium carbonate and a preferred solvent is DMF.

15           The alkenes, arylalkenes, arylalkynes and alkynes so formed can be reduced, for example, by hydrogenation with a metal catalyst and hydrogen, to an alkyl or arylalkyl compound of this invention and a alkyne or arylalkyne can be reduced to a alkene, arylalkene, arylalkane or alkane with under catalytic hydrogenation conditions as discussed herein or with  
20           an deactivated metal catalyst. Catalysts can include, for example, Pd, Pd on Carbon, Pt, PtO<sub>2</sub> and the like. Less robust catalysts (deactivated)

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include such thing as Pd on BaCO<sub>3</sub> or Pd with quinoline or/and sulfur.

An alternative method for alkylation of the amine nitrogen is reductive alkylation. This process, well known in the art, allows treatment of the secondary amine with an aldehyde or ketone in the presence of a reducing agent such as borane, borane:THF, borane:pyridine, lithium aluminum hydride. Alternatively, reductive alkylation can be carried out under hydrogenation conditions in the presence of a metal catalyst. Catalysts, hydrogen pressures and temperatures are discussed and are well known in the art. A preferred reductive alkylation catalyst is borane:pyridine complex.

In the case where an intermediate is a carboxylic acid, standard coupling reactions well known in the art can be used to form the compounds of this invention including protected intermediates. For example, the acid can be converted into an acid chloride, mixed anhydride or activated ester and reacted with an alcohol, amine, hydroxylamine or a protected hydroxylamine in the presence of base to form the amide, ester, hydroxamic acid, protected hydroxamic acid. This is the same product as discussed above. Bases are discussed above and include N-methyl-morpholine, triethylamine and the like.

Coupling reactions of this nature are well known in the art and especially the art related to peptide and amino acid chemistry. Removal of the protecting group can be accomplished, if desired, using standard hydrolysis conditions such as base

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hydrolysis or exchange or acid exchange or hydrolysis as discussed.

The Schemes and/or discussion also illustrate conversion of a carboxylic acid protected as an ester or amide into an hydroxamic acid derivative such as a O-arylalkylether or O-cycloalkoxyalkylether group such as the THP group. Methods of treating an acid or acid derivative with hydroxylamine or a hydroxylamine derivative to form a hydroxamic acid or hydroxamate derivative are discussed above. Hydroxylamine can be used in an exchange reaction by treatment of a precursor compound where the carboxyl is protected as an ester or amide with one or more equivalents of hydroxylamine hydrochloride or hydroxylamine at room temperature or above to provide a hydroxamic acid directly. The solvent or solvents, usually protic or protic solvent mixtures such as those listed herein.

This exchange process can be further catalyzed by the addition of additional acid. Alternatively, a base such as a salt of an alcohol used as a solvent, for example, sodium methoxide in methanol, can be used to form hydroxylamine from hydroxylamine hydrochloride in situ which can exchange with an ester or amide. As mentioned above, exchange can be carried out with a protected hydroxylamine such as tetrahydropyranyl-hydroxyamine (THPONH<sub>2</sub>), benzylhydroxylamine (BnONH<sub>2</sub>), O-(trimethylsilyl)hydroxylamine and the like, in which case the compounds formed are tetrahydropyranyl (THP), benzyl (Bn) or TMS hydroxamic acid derivatives. Removal of the protecting groups when desired, for example, following further

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transformations in another Part of the molecule or following storage, can be accomplished by standard methods well known in the art such as acid hydrolysis of the THP group as discussed above or reductive  
5 removal of the benzyl group with hydrogen and a metal catalyst such as palladium, platinum, palladium on carbon or nickel.

alpha-Amino acids or alpha-hydroxy carboxylic acids or protected carboxylic acids,  
10 hydroxamates or hydroxamic acid derivatives or intermediates (precursors) of this invention can be prepared by displacing, for example, a halogen, sulfate ester or other electrophile, from the alpha carbon of an acid or a derivative as listed. Methods  
15 for the halogenation of acids, esters, acid chlorides and like are well known in the art and include, for example, the HVZ reaction, treatment with  $\text{CuCl}_2$ , N-bromo- or N-chloro-succinimide,  $\text{I}_2$ , carbon tetraiodide or bromide and the like. The halogen can  
20 be displaced with a nucleophile in an  $\text{SN}_2$  reaction. Nucleophiles can include hydroxide, ammonia or amines.

The aryl or heteroaryl carboxylic acids of this invention where Y is 0 and z is 1 can be  
25 prepared from heteroaryl or aryl fused lactones. An example of a fused lactone is phthalide. A preferred starting material is phthalide. This compound can be treated with an thiol, thiolate or metal -SH in order to undergo a  $\text{SN}_2$  displacement at the methylene carbon  
30 to provide a sulfide or thiol compound of this invention or intermediate to a compound of this invention. A preferred thiol is 4-phenoxy-benzenethiol that is used in the presence of

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potassium carbonate as a preferred base. The sulfide can be oxidized, before or after conversion of the acid to a hydroxamate or hydroxamic acid, to a sulfone of this invention. A preferred oxidizing agent is meta-chloroperbenzoic acid.

A preferred acid activating group is the chloride prepared by reaction of an acid with oxalyl chloride as a preferred reagent. A phthalide or a heteroaryl analog of a phthalide can be treated with a Lewis acid such as zinc chloride or zinc bromide along with a halogenating reagent such as phosphorus trichloride or thionyl bromide or the like to form an ortho-(haloalkyl)-aryl acid or ortho-(haloalkyl)-heteroaryl acid derivative. Examples include bromomethyl acid bromides and chloromethyl acid chlorides. These carboxylic acids can be derivatized with protecting groups, hydroxamic acids or hydroxamic acid precursors (hydroxamates) or hydrolyzed to the acid as required. A preferred hydroxamate forming reagent is O-(trimethylsilyl)hydroxylamine (TMS-hydroxylamine) and removal of the TMS protecting group is preferably accomplished by acid hydrolysis using hydrochloric acid.

Displacement ( $SN_2$ ) of the halogen in this example by a thiol in the presence of base or a preformed thiolate can be accomplished as discussed and/or shown and as is well known in the art. Again, oxidation of the sulfide can be carried out before or after derivatization of the carboxylic acid as discussed to prepare the hydroxamic acids of this invention. Removal of the protecting groups can be

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carried out using acid hydrolysis or reduction as discussed elsewhere in this document.

The alcohols of this invention can be protected or deprotected as required or desired.

5 Protecting groups can include THP ethers, acylated compounds and various silyl derivatives. These groups, including there protection and removal, are well known in the art.

Examples of bases that can be used include,  
10 for example, metal hydroxides such as sodium, potassium, lithium or magnesium hydroxide, oxides such as those of sodium, potassium, lithium, calcium or magnesium, metal carbonates such as those of sodium, potassium, lithium, calcium or magnesium,  
15 metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, primary (I°), secondary (II°) or tertiary (III°) organic amines such as alkyl amines, arylalkyl amines, alkylarylalkyl amines, heterocyclic amines or heteroaryl amines, ammonium  
20 hydroxides or quaternary ammonium hydroxides. As non-limiting examples, such amines can include triethyl amine, trimethyl amine, diisopropyl amine, methyldiisopropyl amine, diazabicyclononane, tribenzyl amine, dimethylbenzyl amine, morpholine, N-  
25 methylmorpholine, N,N'-dimethylpiperazine, N-ethylpiperidine, 1,1,5,5-tetramethylpiperidine, dimethylaminopyridine, pyridine, quinoline, tetramethylethylenediamine and the like.

Non-limiting examples of ammonium  
30 hydroxides, usually made from amines and water, can include ammonium hydroxide, triethyl ammonium hydroxide, trimethyl ammonium hydroxide, methyldiisopropyl ammonium hydroxide, tribenzyl

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ammonium hydroxide, dimethylbenzyl ammonium hydroxide, morpholinium hydroxide, N-methylmorpholinium hydroxide, N,N'-dimethylpiperazinium hydroxide, N-ethylpiperidinium hydroxide, and the like. As non-limiting examples, quaternary ammonium hydroxides can include tetraethyl ammonium hydroxide, tetramethyl ammonium hydroxide, dimethyldiisopropyl ammonium hydroxide, benzylmethyldiisopropyl ammonium hydroxide, methyl diazabicyclononyl ammonium hydroxide, methyltribenzyl ammonium hydroxide, N,N'-dimethylmorpholinium hydroxide, N,N,N', N', -tetramethylpiperazinium hydroxide, and N-ethyl-N'-hexylpiperidinium hydroxide and the like. Metal hydrides, amide or alcoholates such as calcium hydride, sodium hydride, potassium hydride, lithium hydride, sodium methoxide, potassium tert-butoxide, calcium ethoxide, magnesium ethoxide, sodium amide, potassium diisopropyl amide and the like can also be suitable reagents. Organometallic deprotonating agents such as alkyl or aryl lithium reagents such as methyl, phenyl, butyl, iso-butyl, sec-butyl or tert-butyl lithium, sodium or potassium salts of dimethylsulfoxide, Grignard reagents such as methylmagnesium bromide or methymagnesium chloride, organocadium reagents such as dimethylcadium and the like can also serve as bases for causing salt formation or catalyzing the reaction. Quaternary ammonium hydroxides or mixed salts are also useful for aiding phase transfer couplings or serving as phase transfer reagents. Preferred base for use in the alkylation reaction is lithium diisopropyl amide as mentioned above.



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Reaction media in general can be comprised of a single solvent, mixed solvents of the same or different classes or serve as a reagent in a single or mixed solvent system. The solvents can be protic, non-protic or dipolar aprotic. Non-limiting examples of protic solvents include water, methanol (MeOH), denatured or pure 95% or absolute ethanol, isopropanol and the like.

Typical non-protic solvents include acetone, tetrahydrofuran (THF), dioxane, diethylether, tert-butylmethyl ether (TBME), aromatics such as xylene, toluene, or benzene, ethyl acetate, methyl acetate, butyl acetate, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, heptane, isooctane, cyclohexane and the like. Dipolar aprotic solvents include compounds such as dimethylformamide (DMF), dimethylacetamide (DMAc), acetonitrile, nitromethane, tetramethylurea, N-methylpyrrolidone and the like.

Non-limiting examples of reagents that can be used as solvents or as Part of a mixed solvent system include organic or inorganic mono- or multi-protic acids or bases such as hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, triethylamine, morpholine, N-methylmorpholine, piperidine, pyrazine, piperazine, pyridine, potassium hydroxide, sodium hydroxide, alcohols or amines for making esters or amides or thiols for making the products of this invention and the like. Room temperature or less or moderate warming (-10°C to 60°C) are the preferred temperatures of the reaction. If desired, the reaction temperature might be about

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-78°C to the reflux point of the reaction solvent or solvents. The preferred solvent for an alkylation reaction is tetrahydrofuran (THF).

Acids are used in many reactions during various synthesis. The Schemes as well as this discussion preparative methods illustrate acid use for the removal of the THP protecting group to produce a hydroxamic acid, removal of a tert-butoxy carbonyl group, hydroxylamine/ester exchange and the like. Acid hydrolysis of carboxylic acid protecting groups or derivatives is well known in the art. These methods, as is well known in the art, can use acid or acidic catalysts. The acid can be mono-, di- or tri-protic organic or inorganic acids. Examples of acids include hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, hydrobromic acid, hydrofluoric acid, carbonic acid, phosphorus acid, p-toluene sulfonic acid, trifluoromethane sulfonic acid, trifluoroacetic acid, difluoroacetic acid, benzoic acid, methane sulfonic acid, benzene sulfonic acid, 2,6-dimethylbenzene sulfonic acid, trichloroacetic acid, nitrobenzoic acid, dinitrobenzoic acid, trinitrobenzoic acid, and the like. They can also be Lewis acids such as aluminum chloride, borontrifluoride, antimony pentafluoride and the like.

Contemplated compounds can include compounds wherein a nitrogen of an amine is acylated to provide, for example, amino acid carbamates. Non-limiting examples of these carbamates are the carbobenzoxy carbonyl (Z, CBZ, benzyloxycarbonyl), iso-butoxycarbonyl and tert-butoxycarbonyl (BOC, t-

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BOC) compounds. The materials can be made, as discussed above, at various stages in the synthesis based on the needs and decisions made by a person skilled in the art using methods well know in the art.

Useful synthetic techniques and reagents include those used in protein, peptide and amino acid synthesis, coupling and transformation chemistry. The use of the tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (Z) as well as their synthesis and removal are examples of such protection or synthesis schemes. Transformations of amino acids, amino esters, amino acid hydroxamates, amino acid hydroxamate derivatives and amino acid amides of this invention or compounds used in this invention is discussed herein or/and shown in the schemes. This includes, for example, active ester or mixed anhydride couplings wherein preferred bases, if required, are tertiary amines such as N-methylmorpholine. Reagents for protection of the amine group of the protected amino acids include carbobenzoxy chloride, iso-butylchloroformate, tert-butoxycarbonyl chloride, di-tert-butyl dicarbonate and the like which are reacted with the amine in non-protic or dipolar aprotic solvents such as DMF or THF or mixtures of solvents.

Removal of protecting groups such as carbamates, silyl groups and benzyl, p-methoxybenzyl, or other substituted benzyl groups or diphenylmethyl (benzhydryl) or triphenylmethyl (trityl) can be carried out at different stages in the synthesis of the compounds of this invention as required by methods selected by one skilled in the art. These

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methods are well known in the art including the amino acid, amino acid coupling, peptide synthesis, peptide mimetic synthesis art. Removal methods can include catalytic hydrogenation, base hydrolysis, carbonyl addition reactions, acid hydrolysis and the like. Both the preparation and removal of protecting groups, for example, carbamates, benzyl groups and/or substituted arylalkyl groups is discussed in Green, T., Protecting Groups in Organic Chemistry, Second ed., John Wiley & Sons, New York (1991). A preferred method of removal of a BOC group is HCl gas in methylene chloride which, following normal workup, provides directly an HCl salt of an aminoacid of this invention.

Sulfone compounds such as those where  $R^1$  is nitrobenzene can be prepared as compounds of this invention by synthesis of a thiol, displacement of an electrophile by the nucleophilic thiol or thiolate and oxidation of the product thiol ether to the sulfone. For example, displacement of the electrophilic group with a nitro-benzene thiol can yield a compound where  $R^1$  is nitrobenzene, whose nitro group can be reduced to provide a useful amino compound wherein  $R^1$  is an aniline. It should be noted that nitrobenzenethiol is an example and not to be considered as limiting or required. Oxidation of the thioether product can be carried out as discussed below when desired.

The reduction of nitro groups to amines is well known in the art with a preferred method being hydrogenation. There is usually a metal catalyst such as Rh, Pd, Pt, Ni or the like with or without an additional support such as carbon, barium carbonate

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and the like. Solvents can be protic or non-protic pure solvents or mixed solvents as required. The reductions can be carried out at atmospheric pressure to a pressure of multiple atmospheres with  
5 atmospheric pressure to about 40 pounds per square inch (psi) preferred.

The resulting amino group can be alkylated if desired. It can also be acylated with, for example, an aroyl chloride, heteroaryl chloride or  
10 other amine carbonyl forming agent to form an R<sup>1</sup> amide of this invention. The amino sulfone or thioether can also be reacted with a carbonic acid ester chloride, a sulfonyl chloride, a carbamoyl chloride or an isocyanate to produce the  
15 corresponding carbamate, sulfonamides, or ureas of this invention. Acylation of amines of this type are well known in the art and the reagents are also well known.

Usually these reactions are carried out in  
20 aprotic solvents under an inert or/and dry atmosphere at about 45°C to about -10°C. An equivalent of a non-competitive base is usually used with sulfonyl chloride, acid chloride or carbonyl chloride reagents. Following or before this acylation step,  
25 synthesis of the hydroxamic acid products of this invention can proceed as discussed.

Other thiol reagents can also be used in the preparation of compounds of this invention. Examples are fluoroaryl, fluoroheteroaryl, azidoaryl  
30 or azidoheteroaryl or heteroaryl thiol reagents. These thiols can be used as nucleophiles to as discussed above. Oxidation to the corresponding sulfone can then be carried out.

The sulfones, if substituted by a hydrazine or substituted hydrazine, can be oxidized to a hydrazone of this invention. The fluoro substituted sulfone can be treated with a nucleophile such as ammonia, a primary amine, a quaternary ammonium or metal azide salt or a hydrazine under pressure if desired, to provide an azido, amino, substituted amino or hydrazino group. Azides can be reduced to an amino group using, for example, hydrogen with a metal catalyst or metal chelate catalyst or by an activated hydride transfer reagent. The amines can be acylated as discussed above.

Methods of preparing useful aminethiol intermediates include protection of an aromatic or heteroaromatic thiol with trityl chloride to form the trityl thiol derivative, treatment of the amine with reagent such as an aromatic or heteroaromatic acid chloride to form the amide, removal of the trityl group, with acid to form the thiol. Acylating agents include benzoyl chloride and trisopropylsilane. The fluorine on the fluorosulfones of this invention can also be displaced with other aryl or heteroaryl nucleophiles for form compounds of this invention. Examples of such nucleophiles include salts of phenols, thiophenols, -OH group containing aromatic heterocyclic compounds or -SH containing heteroaryl compounds. Tautomers of such groups azo, hydrazo, -OH or -SH are specifically included as useful isomers.

A preferred method of preparing intermediates in the synthesis of the substituted sulfones is by oxidation of an appropriate

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acetophenone, prepared from a fluoroacetophenone, with for example, peroxymonosulfate, to form the corresponding phenol-ether. The phenol-ether is converted into its dimethylthiocarbamoyl derivative using dimethylthiocarbamoyl chloride, rearranged into the dimethylthiocarbamoyl derivative with heat to provide the thiol required for preparation of the thioether intermediate discussed and/or shown in the schemes.

10           The compounds of this invention including protected compounds or intermediates can be oxidized to the sulfones as shown in the schemes and/or discussed above. The selection of the stage of the alternative synthesis to implement this conversion of sulfides into the sulfones or sulfoxides can be carried out by one skilled in the art.

Reagents for this oxidation process may, in a non-limiting example, include peroxymonosulfate (OXONE®), hydrogen peroxide, meta-chloroperbenzoic acid, perbenzoic acid, peracetic acid, perlactic acid, tert-butyl peroxide, tert-butyl hydroperoxide, tert-butyl hypochlorite, sodium hypochlorite, hypochlorous acid, sodium meta-periodate, periodic acid, ozone and the like. Protic, non-protic, dipolar aprotic solvents, either pure or mixed, can be chosen, for example, methanol/water. The oxidation can be carried out at temperature of about -78° to about 50° degrees centigrade and normally selected from a range -10°C to about 40°C.

30           Preparation of the sulfones can also be carried out in two steps by the oxidation of a sulfide to a sulfoxide followed by oxidation of the sulfoxide to the sulfone. This can occur in one pot

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or by isolation of the sulfoxide. This latter oxidation can be carried out in a manner similar to the oxidation directly to the sulfone except that about one equivalent of oxidizing agent can be used preferably at a lower temperature such as about zero degrees C. Preferred oxidizing agents include peroxymonosulfate and meta-chloroperbenzoic acid.

A sulfonamide of this invention can be prepared in a similar manner using methods and procedures discussed hereinbefore. Aryl, substituted aryl, heteroaryl or substituted heteroaryl dicarboxylic anhydrides, imides (e.g., phthalic anhydrides or imides), their sulfonyl analogs or mixed carboxylic-sulfonic acid amides, imides (e.g., 1,2-benzenethiazole-3(2H)-one 1,1-dioxides) or anhydrides are useful starting material substrates. Reactions utilizing such substrates can be carried out before or after changes in the substitution patterns of the aryl or heteroaryl rings are made.

The sulfonamides can also be prepared from heterocyclic compounds such as saccharine, saccharine analogs and saccharine homologs. Such compounds and methods are well known in the literature. For example, alkylation of sodium saccharine followed by ring opening or ring opening followed by alkylation permits coupling to form a protected hydroxamic acid derivative such as a THP (tetrahydropyranyl) or TMS (trimethylsilyl) derivative. Hydrolysis of the protecting group provides the hydroxamic acid. The sulfonamide nitrogen can be further alkylated, acylated or otherwise treated to form various compounds of, for example, Formula VI at this stage of prior to coupling and deprotection.



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As a non-limiting example, treatment of a mixed sulfonic/carboxylic anhydride (2-sulfobenzoic acid cyclic anhydride) with an alcohol or the salt of an alcohol or a protected hydroxamic acid provides a  
5 ring opened carboxylic acid derivative (ester or anhydride, respectively) as a sulfonic acid or salt. The carboxylic acid derivative so prepared is a product of this invention, and can be converted by standard procedures with reagents such as thionyl  
10 chloride, phosphorus pentachloride or the like into a sulfonylhalide.

Reaction of the sulfonylhalide with a primary amine, secondary amine or ammonia with or without added base provides a sulfonamide or  
15 sulfonimide of this invention, a sulfonamide that can be alkylated to produce a sulfonamide of this invention or an intermediate to a sulfonamide of this invention. These imides or amides of sulfonamides can be alkylated as desired before or after opening  
20 to a benzoic acid substituted sulfonamide or phenylacetic acid substituted sulfonamide.

Compounds prepared as above with protected carboxyl groups are readily converted by exchange, combination exchange/hydrolysis or hydrolysis-  
25 coupling processes into the hydroxamic acids of this invention. The exchange/conversion of esters, amides and protected hydroxylamines (protected hydroxamic acids) into hydroxamic acids is discussed herein. For example, a sulfonamide-ester can be hydrolyzed to  
30 a carboxylic acid that is coupled via a benzotriazole active ester with a THP-hydroxylamine reagent and then deprotected. Phenylacetic acid analogs of the above sulfo benzoic acid compounds can also be used

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in processes similar to those above to prepare the corresponding phenylacetic-derived compounds of this invention.

Aryl or heteraryl 5- or 6-membered ring  
5 thiolactones or dithiolactones are also desirable starting materials for the preparation of compounds of this invention. Such thiolactones can be opened to form protected carboxylic acid derivatives such as esters, amides or hydroxylamides before or after  
10 changes in the substitution patterns of the aryl or heteroaryl rings are made. Oxidation of the thiol function can be achieved prior to or following substitution changes depending upon the needs and wishes of the skilled chemist. Sulfur compounds can  
15 also be oxidized directly to sulfonyl chloride compounds using oxidizing agents whose mechanism involved putative positive chlorine species. Oxidizing agents and methods are discussed hereinabove. The sulfonic acid derivatives so  
20 obtained are then converted into the sulfonamides of this invention as previously discussed.

Changes in substitution patterns on the rings of the compounds of this invention can be carried out by processes well known in the art. Non-  
25 limiting examples of such processes include diazonium chemistry, aromatic ring substitution reactions or addition-elimination sequences, metallation reactions and halogen metal exchange reactions.

A substituted or unsubstituted aryl or  
30 heteroaryl sulfonic acid, sulfonic acid derivative or sulfonamide of this invention can be prepared starting with a halo-sulfonic acid or a sulfonic acid substituted in such a manner that the corresponding

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anion can be reacted with carbon dioxide, a carbonyl compound, isocyanate, a halogenating reagent, alkylating reagent, acylating reagent, a protected hydroxylamine isocyanate or isothiocyanate derivative  
5 to form a compound of this invention or an intermediate to a compound of this invention. An anion can be formed via, for example, direct metallation or metal-halogen exchange. The substituted or unsubstituted aryl or heteroaryl  
10 sulfonic acid, sulfonic acid derivative or sulfonamide can be prepared by sulfonation or chlorosulfonation of the substituted or unsubstituted aryl or heteroaryl compound. Metallation reactions as well as halogen-metal exchange reactions to form  
15 the salts of the corresponding anions or complexed anions can be carried out by direct treatment with a metal such as lithium, sodium, potassium, palladium, platinum or their complexes, and the like or treatment with a strong base such as tert-butyl  
20 lithium, sec-butyl lithium, and the like as discussed above. These intermediates are then quenched with a reagent such as is discussed elsewhere. The resulting carboxylic acids or carboxylic acid derivatives are converted into the sulfonamides of  
25 this invention by methods and processes known in the art and discussed herein.

Salts of the compounds or intermediates of this invention are prepared in the normal manner wherein acidic compounds are reacted with bases such  
30 as those discussed above to produce metal or nitrogen containing cation salts. Basic compounds such as amines can be treated with an acid to form an amine salt.

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It is noted that some compounds of this invention can be synthesized by biochemical processes, including mammalian metabolic processes. For example, methoxy groups can be converted by the  
5 liver in situ into alcohols and/or phenols. Where more than one methoxy group is present, either or both groups can be independently metabolized to hydroxy compounds.

Compounds of the present can possess one or  
10 more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional  
15 processes well known in the art, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base.

Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric,  
20 ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves  
25 the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers.

Still another available method involves synthesis of covalent diastereoisomeric molecules, e.g., esters, amides, acetals, ketals, and the like,  
30 by reacting compounds of Formula I with an optically active acid in an activated form, a optically active diol or an optically active isocyanate. The synthesized diastereoisomers can be separated by

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conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. In some cases hydrolysis to the parent  
5 optically active drug is not necessary prior to dosing the patient since the compound can behave as a prodrug. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.

10 In addition to the optical isomers or potentially optical isomers discussed above, other types of isomers are specifically intended to be included in this discussion and in this invention. Examples include cis isomers, trans isomers, E  
15 isomers, Z isomers, syn- isomers, anti- isomers, tautomers and the like. Aryl, heterocyclo or heteroaryl tautomers, heteroatom isomers and ortho, meta or para substitution isomers are also included as isomers. Solvates or solvent addition compounds  
20 such as hydrates or alcoholates are also specifically included both as chemicals of this invention and in, for example, formulations or pharmaceutical compositions for drug delivery.

Where a substituent is designated as, or  
25 can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the  
30 overall activity and/or synthesis procedure. For example, two hydroxyl groups, two amino groups, two thiol groups or a mixture of two hydrogen-heteroatom

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groups on the same carbon are known not to be stable without protection or as a derivative.

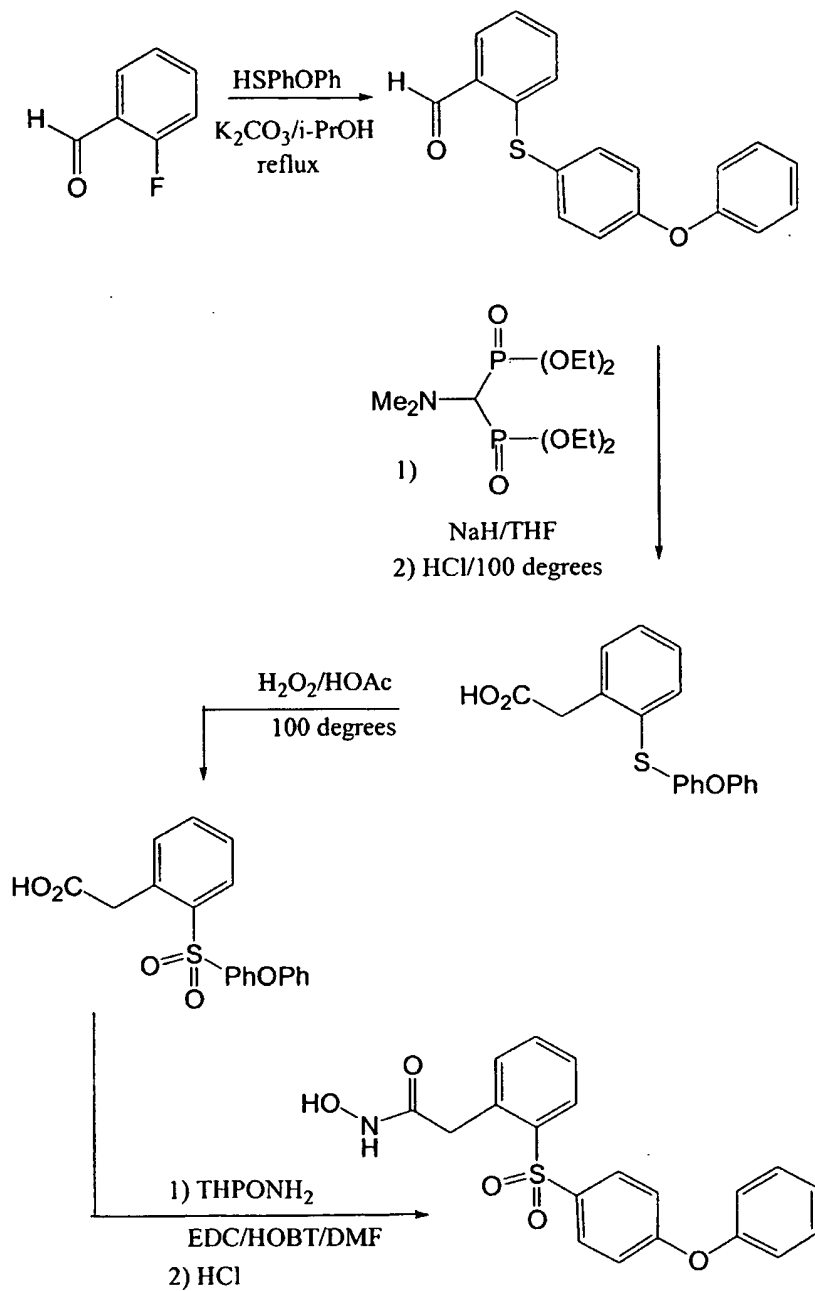
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions can not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Other compounds of this invention that are acids can also form salts. Examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases or basic quaternary ammonium salts.

In some cases, the salts can also be used as an aid in the isolation, purification or resolution of the compounds of this invention.

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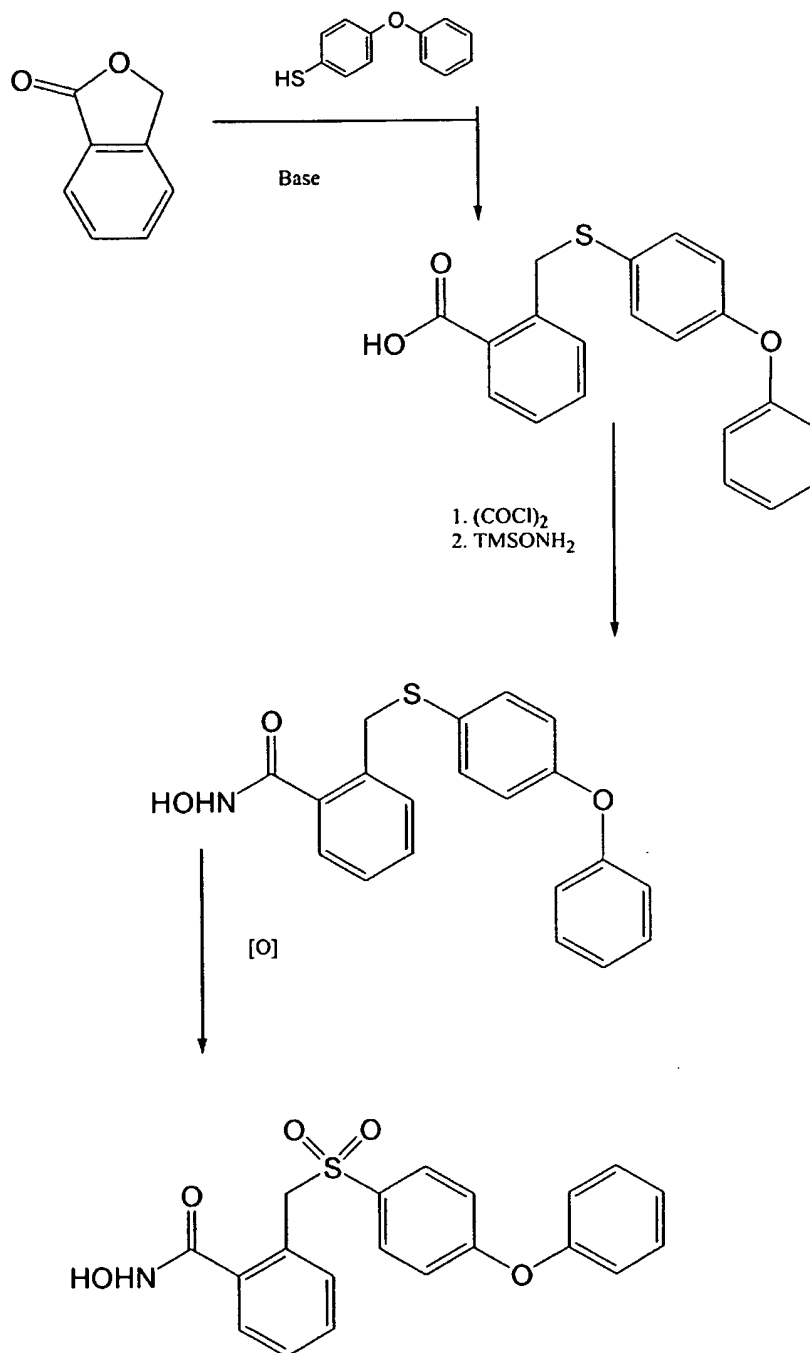
## Scheme 1



## Example 1

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## Scheme 2

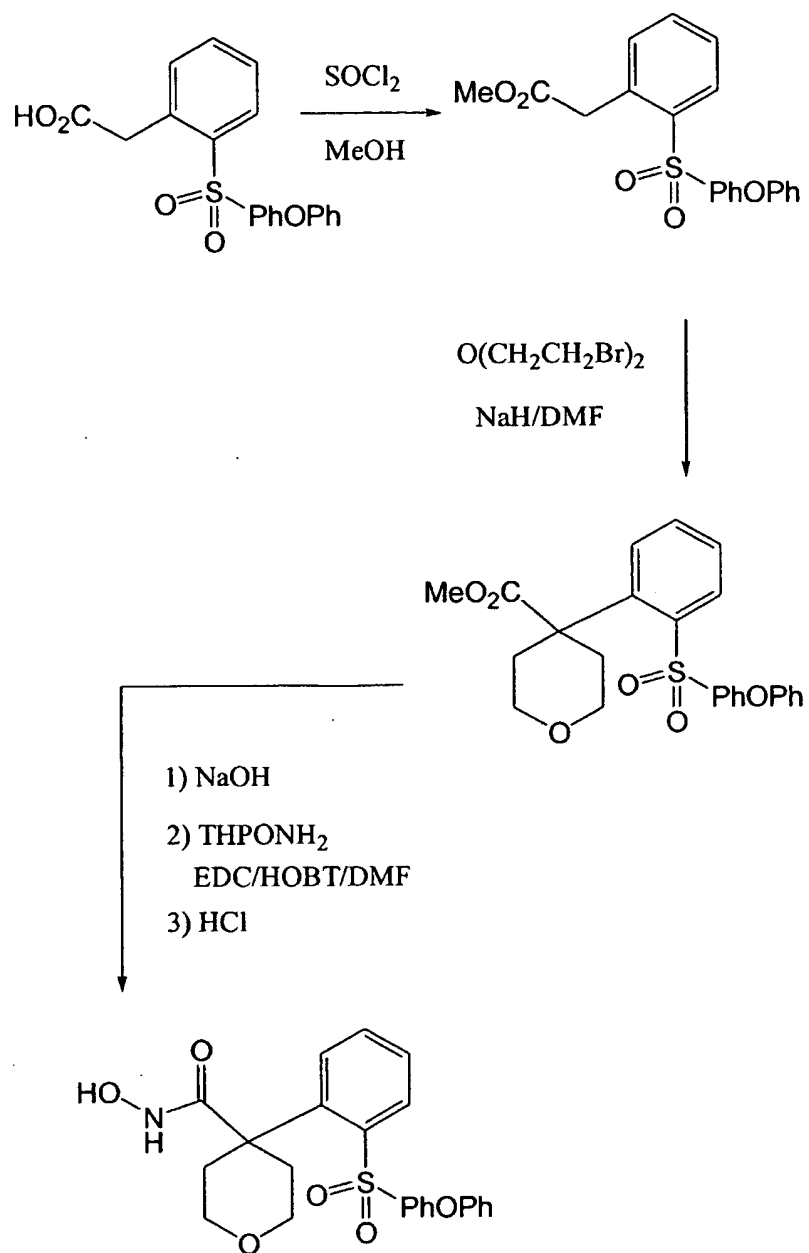


## Example 2



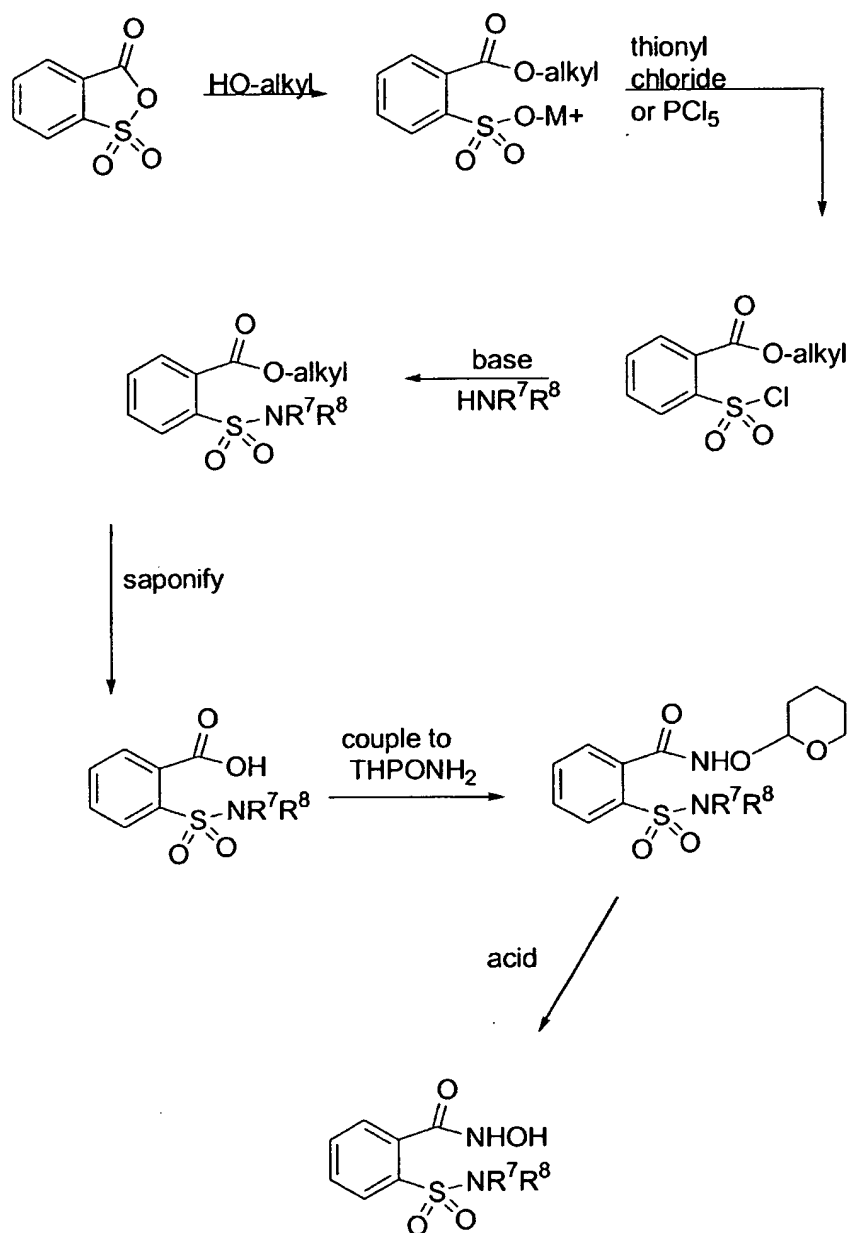
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## Scheme 3



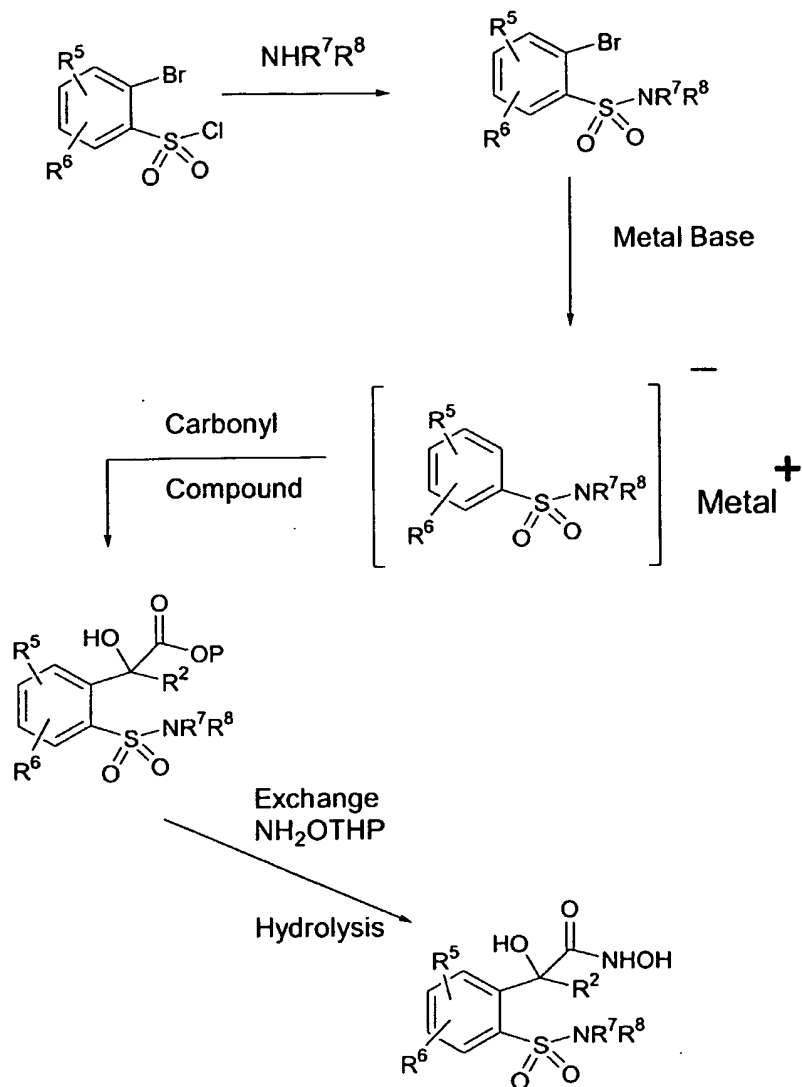
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## Scheme 4

 $\text{R}^7$  and  $\text{R}^8$  are as in Formula VI

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## Scheme 5



$\text{R}^2$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ , and  $\text{R}^8$  are as discussed for

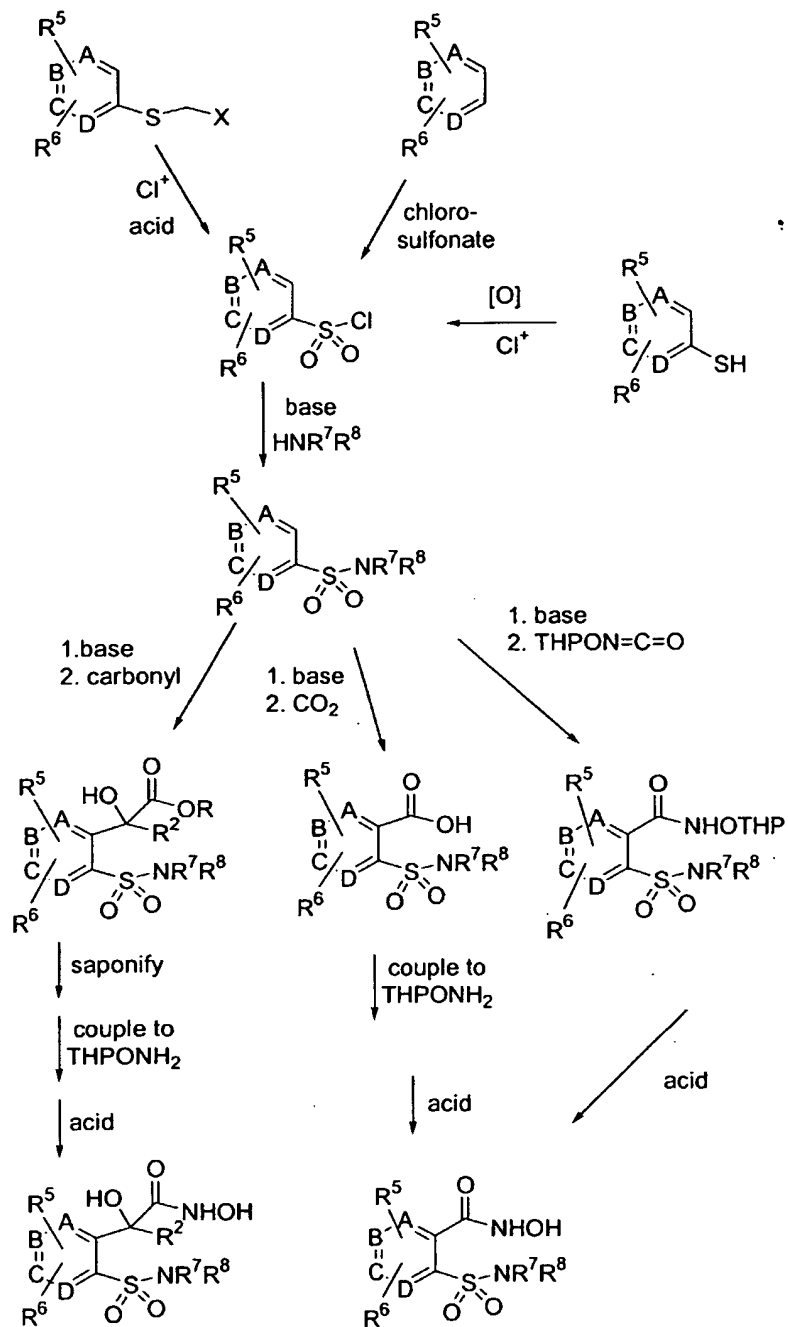
Formula VI, and

P = is a selectively removable protecting group

as discussed for  $\text{R}^{20}$

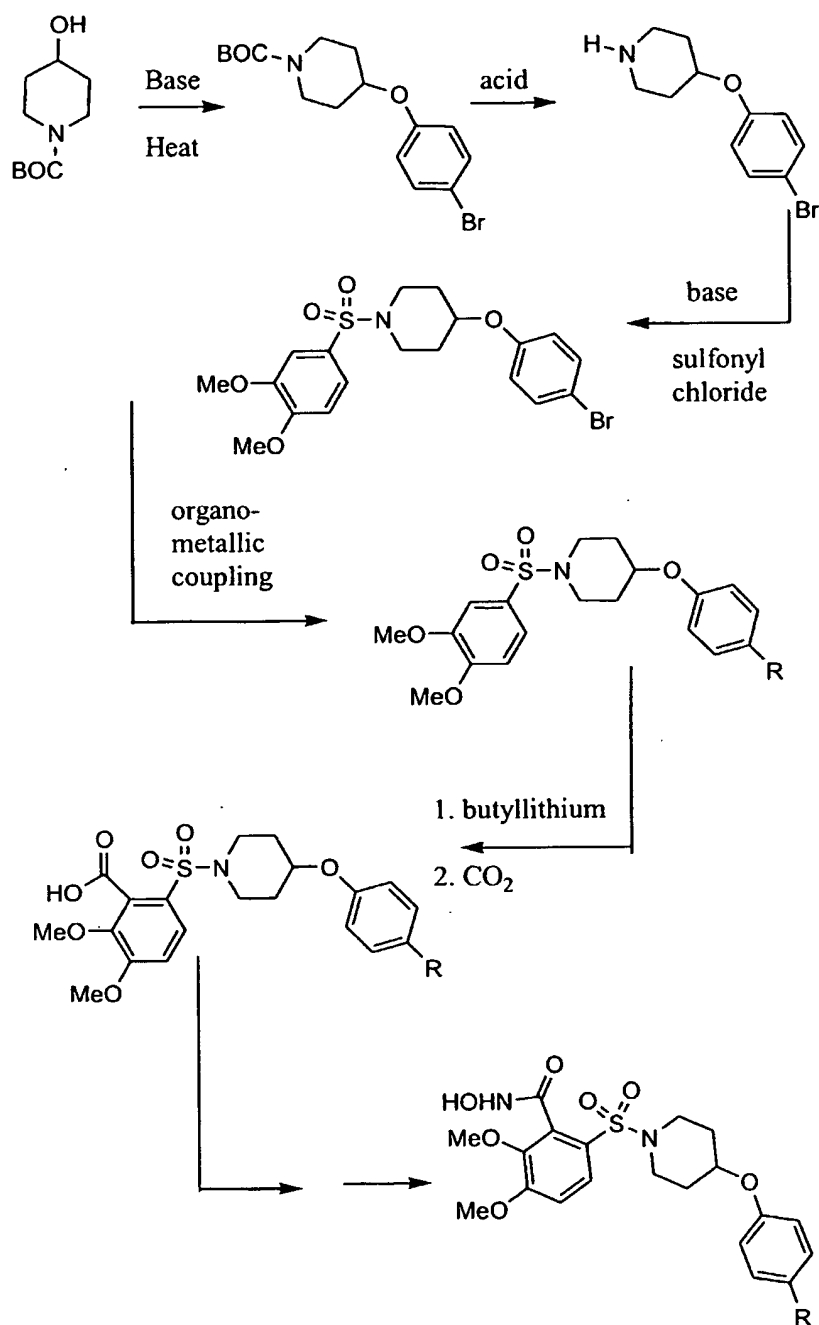
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## Scheme 6

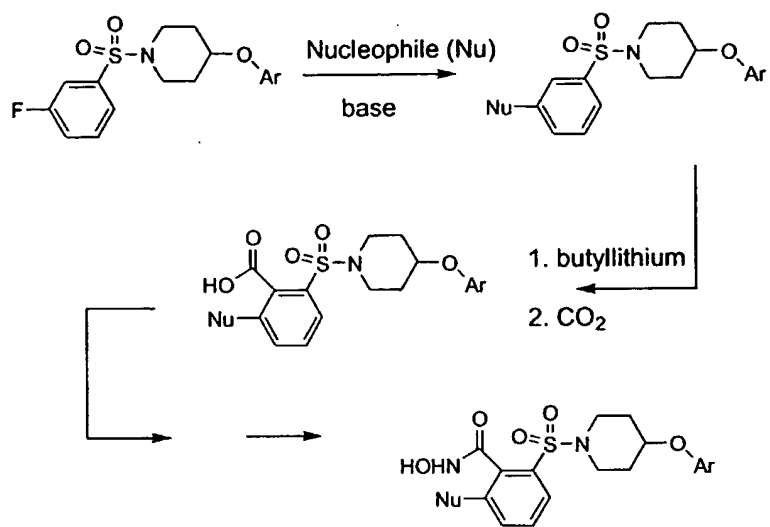
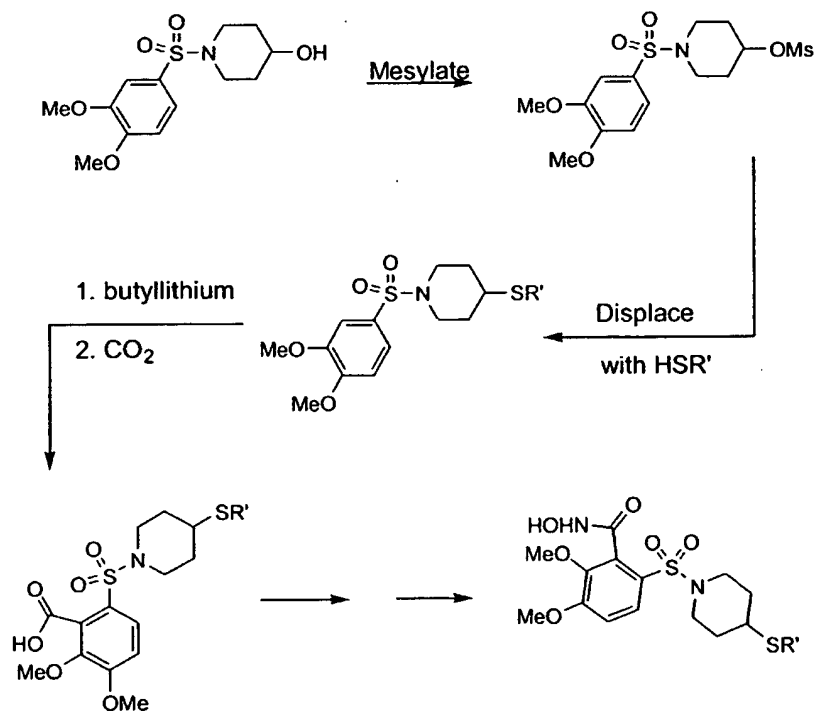

 $R^2, R^5, R^6, R^7, R^8, A, B, C,$  and  $D$ 

are as discussed for Formula VI

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**Scheme 7**

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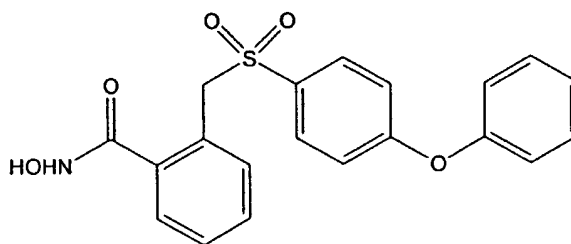
**Schem 8****Scheme 9**

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Best Mode for Carrying Out the Invention

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its  
5 fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limiting of the remainder of the disclosure in any way whatsoever.

- 10 Example 1: N-hydroxy-2-[[[4-phenoxyphenyl)-sulfonyl]methyl]benzamide



- 15 Part A: To a solution of phthalide (6.30 g, 47.0 mmol) in DMF (100 mL) was added K<sub>2</sub>CO<sub>3</sub> (10.0 g, 49.4 mmol) and 4-(phenoxy)benzenethiol (9.59 g, 49.4 mmol) and the solution was heated to one hundred degrees Celsius for 2 hours. The solution was  
20 diluted with H<sub>2</sub>O and acidified with 1N HCl to pH = 1. The resulting tan solid was collected and washed with H<sub>2</sub>O. The solid was dissolved into ethyl ether and dried over MgSO<sub>4</sub>. Concentration *in vacuo* followed by recrystallization (ethyl ether/hexane) provided the  
25 sulfide as a white solid (9.12 g, 58 %). MS(CI) MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>S: 337, found 337. Analytical calculation for C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>S: C, 71.41; H, 4.79; S, 9.53. Found: C, 71.28; H, 4.67; S, 9.19.

- Part B: To a solution of the sulfide of Part A  
30 (3.00 g, 8.92 mmol) in dichloromethane (28 mL) and

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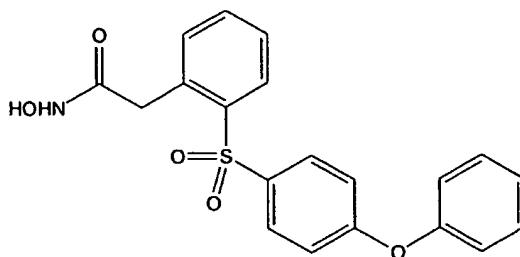
DMF (1 drop) was added oxalyl chloride (1.08 mL, 12.4 mmol) and the solution was stirred for one hour. After concentration in vacuo, the residue was dissolved into dichloromethane (16 mL) and the solution was cooled to zero degrees Celsius. Tetramethylsilyl hydroxylamine (2.55 mL, 20.8 mmol) was added and the solution was stirred for 1.5 hours. The solution was diluted with dichloromethane and washed with 1 N HCl, H<sub>2</sub>O and saturated NaCl and dried over MgSO<sub>4</sub>. Chromatography (on silica, ethyl acetate/hexane/ toluene) provide the hydroxylamine as a clear paste (970 mg, 31%).

Part C: To a solution of the hydroxylamine of Part B (970 mg, 2.76 mmol) in dichloromethane (25 mL) cooled to zero degrees Celsius was added 3-chloroperbenzoic acid (60%, 2.14 g, 7.45 mmol) and the solution was stirred for 3 hours at ambient temperature. The solution was diluted with ethyl ether and washed with saturated Na<sub>2</sub>SO<sub>3</sub>, saturated NaHCO<sub>3</sub> and saturated NaCl and dried over MgSO<sub>4</sub>. Reverse phase chromatography (on silica, acetonitrile/H<sub>2</sub>O) provided the title compound as a white solid (345 mg, 33%). MS(CI) MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>17</sub>NO<sub>5</sub>S: 384, found 384. Analytical calculation for C<sub>20</sub>H<sub>17</sub>NO<sub>5</sub>S•0.3H<sub>2</sub>O: C, 61.70; H, 4.56; N, 3.60; S, 8.25. Found: C, 61.74; H, 4.42; N, 3.61; S, 8.31.

Example 2: N-hydroxy-2-[(4-phenoxyphenyl)-sulfonyl]benzeneacetamide



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Part A: To a solution of 4-(phenoxy)-  
benzenethiol (6.06 g, 30.0 mmol) and  $K_2CO_3$  (4.55 g,  
5 33.0 mmol) in isopropanol (30 mL) was added 2-  
fluorobenzaldehyde (3.2 mL, 30.0 mmol). The solution  
was refluxed for 20 hours. The reaction was quenched  
by the addition of ice- $H_2O$  and was extracted with  
 $CHCl_3$ . The organic layer was dried over  $MgSO_4$ .  
10 Filtration through a pad of silica gel provided the  
sulfide as a yellow solid (7.43 g, 81 %).

Part B: A solution of NaH (60 % dispersion in  
mineral oil, washed with hexane, 264 mg, 6.6 mmol) in  
THF (12 mL) was cooled to zero degrees Celsius and  
15 tetraethyl dimethylammoniummethylenediphosphonate  
(1.99 g, 6.0 mmol) was added. The solution was  
warmed to ambient temperature and the sulfide of Part  
A (1.84 g, 6.0 mmol) was added. The solution was  
stirred for 4 hours at ambient temperature. The  
20 solution was extracted with ethyl acetate and washed  
with  $H_2O$  and dried over  $MgSO_4$ . Concentration *in vacuo*  
provided a brown oil which was dissolved in 6M HCl  
(10 mL) and the solution was heated to one hundred  
degrees Celsius for 1 hour. The solution was  
25 extracted with  $CHCl_3$  and the organic layer was dried  
over  $MgSO_4$ . Concentration *in vacuo* provided the acid  
as an oil (918 mg, 48 %).

Part C: To a solution of the acid of Part B  
(918 mg, 3 mmol) in acetic acid (30 mL) was added 30%

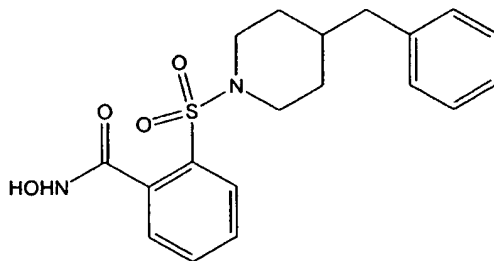
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hydrogen peroxide (1.2 mL, 12 mmol) and the solution was heated to one hundred degrees Celsius for 40 minutes. The solution was lyophilized and chromatography (hexane/ethyl acetate) provided the sulfone as a foam (697 mg, 63 %).

Part D: To a solution of the sulfone of Part C (695 mg, 1.89 mmol) in acetonitrile (2 mL) was added O-tetrahydropyranyl hydroxylamine (270 mg, 2.3 mmol). After 5 minutes EDC (442 mg, 2.3 mmol) was added and the solution was stirred for 3 hours. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub>. Chromatography (on silica gel, ethyl acetate/hexane) provided the THP-ether as a white foam (688 mg, 77 %).

Part E: To a solution of the THP-ether of Part D (565 mg, 1.2 mmol) in methanol (10 mL) was added p-toluenesulfonic acid (25 mg) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated *in vacuo* and chromatography (chloroform/methanol) provided the title compound as a white solid (339 mg, 74 %).

Example 3: N-hydroxy-2-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]benzamide



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Part A: To a solution of 2-chlorosulfonyl-benzoic acid ethyl ester, prepared per Nagasawa, et. al. J. Med. Chem. 1995, 38, 1865-1871, (5.80 g, 23.0 mmol) in acetonitrile (50 mL) was added 4-benzylpiperidine (4.38 mL, 25 mmol), triethylamine (3.78 mL, 27 mmol) and 4-dimethylaminopyridine (50 mg). The solution was stirred for 4 hours at ambient temperature and concentrated *in vacuo*. The residue was dissolved into 1N HCl and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and filtered through a pad of silica gel to provide the sulfonamide as an oil (7.45 g, 84 %).

Part B: To a solution of the sulfonamide of Part A (1.08 g, 2.80 mmol) in methanol (50 mL) and H<sub>2</sub>O (20 mL) was added KOH (2 g) and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated *in vacuo* and the remaining aqueous solution was acidified with 1N HCl. The solution was extracted with chloroform and the organic layer was dried over MgSO<sub>4</sub> and filtered through a pad of silica gel. Concentration *in vacuo* provided the acid as a white foam (996 mg, quantitative yield).

Part C: To a solution of the acid of Part B (415 mg, 1.2 mmol) in acetonitrile (2 mL) was added O-tetrahydropyranyl hydroxylamine (200 mg, 1.7 mmol). After the solution was stirred for 5 minutes EDC (325 mg, 1.7 mmol) was added and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated *in vacuo* and the residue was dissolved into H<sub>2</sub>O and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub>. Chromatography

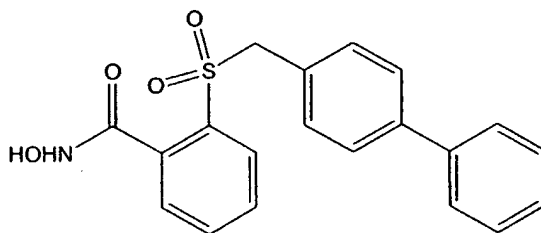
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(on silica, ethyl acetate/hexane) provided the THP-ether as a white solid (437 mg, 82 %).

Part D: To a solution of the THP-ether of Part C (437 mg, 0.98 mmol) in methanol (5 mL) was added p-toluenesulfonic acid (40 mg) and the solution was stirred for 1 hour at ambient temperature. The solution was concentrated *in vacuo*. Chromatography (ethyl acetate, 1% NH<sub>4</sub>OH) provided the title compound as an oil (122 mg, 34 %).

10

Example 4: 2-[[[1,1'-biphenyl]-4-ylmethyl)-sulfonyl]-N-hydroxybenzamide



15

Part A: To a solution of thiosalicylic acid (5.00 g, 32.4 mmol) and 4-phenylbenzyl chloride (6.57 g, 32.4 mmol) in ethanol (81 mL) and H<sub>2</sub>O (40 mL) was added K<sub>2</sub>CO<sub>3</sub> (4.48 g, 32.4 mmol) and the solution was heated to reflux for 2 hours. Upon cooling to ambient temperature a white solid formed. To this mixture is added 1N HCl (200 mL) and vacuum filtration provided the sulfide as a white solid (7.32 g, 70 %).

Part B: To a solution of the sulfide of Part A (1.00 g, 3.12 mmol) in formic acid (17 mL) heated to fifty degrees Celsius was added 30% hydrogen peroxide (1.16 mL). The solution was stirred at fifty-five degrees Celsius for 3 hours followed by 40 hours at ambient temperature. The solution was concentrated

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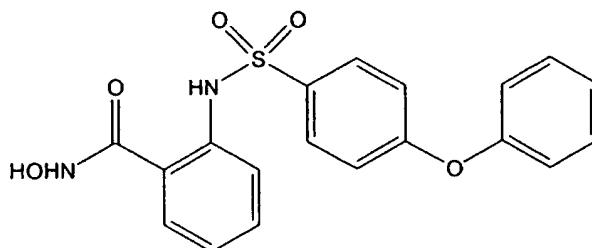
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and reverse phase chromatography (acetonitrile/H<sub>2</sub>O) provided the sulfone as a white solid (500 mg, 45 %).

Part C: To a solution of the sulfone of Part B (500 mg, 1.42 mmol) in DMF (2.8 mL) was added O-tetrahydropyranyl hydroxylamine (173 mg, 1.48 mmol), N-hydroxybenzotriazole (211 mg, 1.56 mmol) and EDC (299 mg, 1.56 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated *in vacuo* and the residue was dissolved into H<sub>2</sub>O. The solution was extracted with ethyl acetate and the organic layer was washed with 1 N HCl, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O and saturated NaCl and dried over MgSO<sub>4</sub>. Concentrated *in vacuo* provided the ester as a white solid (571 mg, 89 %). MS(CI) MH<sup>+</sup> calculated for C<sub>25</sub>H<sub>25</sub>NO<sub>5</sub>S: 452, found 452.

Part D: To a solution of the ester of Part C (570 mg, 1.26 mmol) in methanol (10 mL) was added p-toluenesulfonic acid (15 mg) and the solution was stirred at ambient temperature for 1.5 hours. The solution was concentrated *in vacuo* and reverse phase chromatography (acetonitrile/H<sub>2</sub>O) provided the title compound as a white solid (244 mg, 53 %). MS(EI) M<sup>+</sup> calculated for C<sub>20</sub>H<sub>17</sub>NO<sub>4</sub>S: 367, found 367. Analytical calculation for C<sub>20</sub>H<sub>17</sub>NO<sub>4</sub>S: C, 65.38; H, 4.66; N, 3.81. Found: C, 65.01; H, 4.64; N, 4.04.

Example 5: N-hydroxy-2-[[ (4-phenoxyphenyl) -sulfonylamino]benzamide



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Part A: To a solution of isatoic anhydride (1.00 g, 6.13 mmol) in acetonitrile (3 mL) was added O-tetrahydropyranyl hydroxylamine (1.56 g, 6.74 mmol) and the solution was heated to reflux for 2 hours. The solution was concentrated in vacuo and recrystallization of the residue (ethyl acetate/hexane) provided the THP-ether as a white solid (760 mg, 52 %). MS(CI)  $MH^+$  calculated for  $C_{12}H_{16}N_2O_3$ : 237, found 237. Analytical calculation for  $C_{12}H_{16}N_2O_3$ : C, 61.00; H, 6.83; N, 11.86. Found: C, 60.82; H, 6.95; N, 11.76.

Part B: To a solution of 4-(phenoxy)benzene sulfonyl chloride, prepared per J. Am. Chem. Soc., 1931, 93, 1112-1115) (341 mg, 1.27 mmol) in pyridine (2 mL) cooled to zero degrees Celsius was added the THP-ether of Part A (300 mg, 1.27 mmol) and the solution was stirred at zero degrees Celsius for 3 hours. The solution was concentrated in vacuo and the residue was dissolved in 1 N HCl and was extracted with ethyl acetate. The organic layer was washed with 1 N HCl,  $H_2O$  and saturated NaCl and dried over  $MgSO_4$ . Chromatography (on silica gel, ethyl acetate/hexane) provided the sulfone as a white solid (321 mg, 54%). MS(CI)  $MH^+$  calculated for  $C_{24}H_{24}N_2O_6S$ : 469, found 469. Analytical calculation for  $C_{24}H_{24}N_2O_6S$ : C, 61.53; H, 5.16; N, 5.98; S, 6.84. Found: C, 61.10; H, 4.93; N, 5.86; S, 6.41.

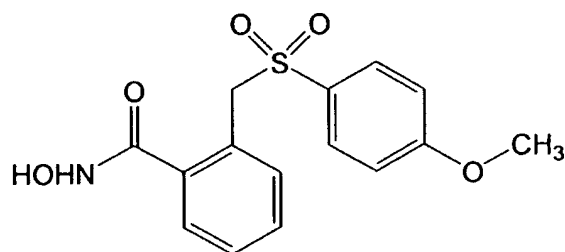
Part C: Into a solution of the sulfone of Part B (320 mg, 0.68 mmol) in methanol (3 mL) cooled to zero degrees Celsius was bubbled HCl gas for 5 minutes. The solution was concentrated in vacuo and the residue was triturated with ethyl ether.

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Collection by vacuum filtration provided the title compound as a pink solid (163 mg, 62 %). MS(CI)  $MH^+$  calculated for  $C_{19}H_{16}N_2O_4S$ : 385, found 385. Analytical calculation for  $C_{19}H_{16}N_2O_6S \cdot 0.2H_2O$ : C, 58.81; H, 4.26; N, 7.22; S, 8.26. Found: C, 58.88; H, 4.37; N, 6.98; S, 7.83.

Example 6 : N-hydroxy-2-[[[4-methoxyphenyl)-  
sulfonylmethyl]benzamide

10



Part A : A 500 mL round bottom flask equipped with magnetic stir bar and  $N_2$  inlet was charged with 1.5 mL (1.7 g, 12.0 mM) 4-methoxybenzenethiol and 2.5 g (10.9 mM) methyl (2-bromomethyl)benzoate in acetone (100 mL). The solution was treated with 1.8 g (13.1 mM) potassium carbonate and heated at  $55^\circ C$  in an oil bath. The reaction mixture was stirred at  $55^\circ C$  for 17 hours, then concentrated *in vacuo*. The residue was partitioned between EtOAc and  $H_2O$ , the layers were separated and the aqueous layer was extracted with EtOAc (1X), the organic phases were combined, washed with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried ( $Na_2SO_4$ ), and concentrated *in vacuo* to yield 3.3 g of product suitable for the next reaction.

Part B : A 500 mL round bottom flask equipped with magnetic stir bar and  $N_2$  inlet was charged with

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3.1 g (10.8 mM) of product from Part A in 90 mL MeOH. The solution was then treated with 15 mL water and 13.9 g (22.6 mM) Oxone®. The reaction mixture was stirred 17 hours, then filtered. The filter cake was washed with MeOH, and the filtrate was concentrated in vacuo. The residue was partitioned between EtOAc and H<sub>2</sub>O; the layers were separated and the aqueous layer was extracted with EtOAc (2X). The organic phases were combined, washed with saturated sodium bicarbonate solution and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo to yield the 3.3 g of crude product. This was chromatographed on silica gel using 25-45% ethyl acetate/hexane to yield 2.1 g of pure product, m/z= 321 (M+H).

Part C : A 250 mL round bottom flask equipped with magnetic stir bar and N<sub>2</sub> inlet was charged with 2.1 g (6.6 mM) of product from Part B in acetic acid (25 mL) and conc. HCl solution (25 mL) and the solution was heated to reflux for a total of 24 hours. The reaction mixture was concentrated in vacuo, then two aliquots of toluene were added and stripped, then dried under high vacuum to yield 2.0 g of product suitable for the next reaction.

Part D : A 2-necked 50 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N<sub>2</sub> inlet was charged with 1.0 mL of DMF in 10 mL CH<sub>2</sub>Cl<sub>2</sub>. The solution was cooled in an ice bath, then treated with 3.5 mL (0.9 g, 6.9 mM) of a 2.0 M oxalyl chloride solution in CH<sub>2</sub>Cl<sub>2</sub>, then with a solution of 1.0 g (3.3 mM) of product from Part C in 5 mL DMF. The bath was removed and the reaction was stirred for 1 hour. That reaction mixture was added to a 2-necked 100 mL round-bottomed flask equipped

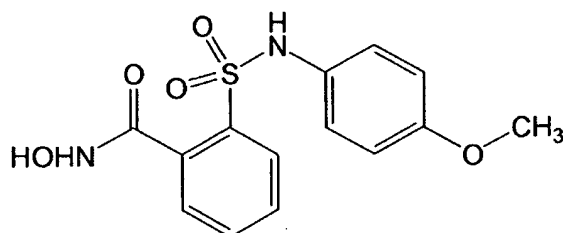


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with addition funnel, thermometer, magnetic stir bar and N<sub>2</sub> inlet and containing a cooled solution of 2.1 mL (1.1 g, 37.7 mM) of 50% aqueous hydroxylamine in THF (25 mL). The bath was then removed and the  
5 reaction mixture was stirred for 2 hours. The reaction was filtered, the filtrate was concentrated in vacuo, the residue was partitioned between EtOAc/water, the layers were separated, the aqueous layer was extracted with EtOAc (1X), the organic  
10 phases were combined and washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to yield 1.3 g of crude product. That material was chromatographed on silica gel using 80% ethyl acetate/hexane to yield 0.5 g of pure product, m/z= 328 (M+Li).

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Example 7 : N-hydroxy-2-[(4-methoxyanilino)-  
sulfonyl]benzamide



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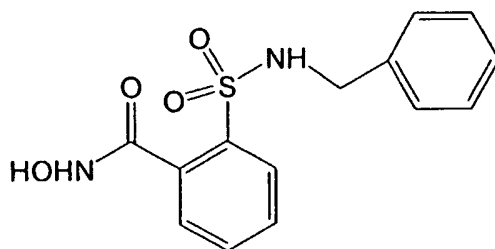
Part A : A 3-necked 100 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N<sub>2</sub> inlet was charged with 0.5 g (4.3 mM) of p-anisidine and 1.8 mL (1.3 g, 12.8 mM)  
25 triethylamine in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The solution was cooled in an ice bath, then treated with a solution of 1.0 g (4.3 mM) methyl (2-chlorosulfonyl)benzoate in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The reaction mixture was stirred for 17 hours, then concentrated in vacuo. The  
30 residue was partitioned between EtOAc and H<sub>2</sub>O, the

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layers were separated and the organic phase was washed with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated *in vacuo* to yield 0.9 g of crude product. This was chromatographed on silica gel using 20-30% ethyl acetate/hexane to yield 0.7 g of pure product,  $m/z = 328$  ( $M+Li$ ).

Part B : A 100 mL round bottom flask equipped with magnetic stir bar and  $\text{N}_2$  inlet was charged with 0.7 g (2.1 mM) of the product from Part A and 0.7 g (10.2 mM) of hydroxylamine hydrochloride in 10 mL MeOH. The reaction was cooled to zero degrees C and charged with 0.4 g (16.4 mM) of sodium metal. After stirring for 17 hours, the reaction was concentrated *in vacuo*, the residue was slurried in 20 mL of water, then acidified using 2 N HCl solution. The aqueous slurry was extracted with EtOAc (3X). The organic layers were combined and washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated *in vacuo* to yield 0.6 g of crude product. The addition of methylene chloride to the crude product precipitated an off-white solid. Filtration gave 0.2 g of pure product,  $m/z = 323$  ( $M+Li$ ).

Example 8 : N-hydroxy-2-[(benzylamino)-  
sulfonyl]benzamide



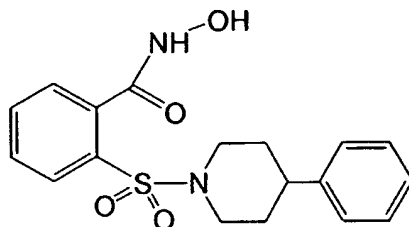
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Part A : A 3-necked 100 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N<sub>2</sub> inlet was charged with 0.5 mL (0.5 g, 4.3 mM) of benzylamine and 1.8 mL (1.3 g, 12.8 mM) triethylamine in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The solution was cooled in an ice bath, then treated with a solution of 1.0 g (4.3 mM) methyl (2-chlorosulfonyl)benzoate in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The reaction mixture was stirred for 2 hours, then concentrated *in vacuo*. The residue was partitioned between EtOAc and H<sub>2</sub>O, the layers were separated and the organic phase was washed with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to yield 0.9 g of crude product. This was chromatographed on silica gel using 20% ethyl acetate/hexane to yield 0.7 g of pure product, m/z= 312 (M+Li).

Part B : A 100 mL round bottom flask equipped with magnetic stir bar and N<sub>2</sub> inlet was charged with 0.7 g (2.1 mM) of the product from Part A and 0.7 g (10.6 mM) of hydroxylamine hydrochloride in 10 mL MeOH. The reaction was cooled to zero degrees C and charged with 0.4 g (17.0 mM) of sodium metal. After stirring for 17 hours, the reaction was concentrated *in vacuo*, the residue was slurried in 20 mL of water, then acidified using 2 N HCl solution. The aqueous slurry was extracted with EtOAc (3X). The organic layers were combined and washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to yield 0.3 g of crude product. The addition of methylene chloride to the crude product precipitated a white solid. Filtration gave 0.1 g of pure product, m/z= 307 (M+H).

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Example 9: Preparation of N-Hydroxy-2-[[4-(phenyl)-  
1-piperidinyl]sulfonyl]benzamide



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Part A: 2-Carboethoxybenzenesulfonyl chloride (3.72 g, 15 mmol) was dissolved in methylene chloride (60 mL). 4-Phenylpiperidine (2.89 g, 18 mmol) was added, followed by triethylamine (2.5 mL, 18 mmol) and 4-(dimethylamino)piperidine (100 mg). After 5 hours, the mixture was diluted with 10 percent aqueous HCl (100 mL). The organic layer was separated and dried over magnesium sulfate. The solution was filtered through a silica pad and concentrated affording the ester sulfonamide as an oil (3.27 g, 63%).

Part B: The ester sulfonamide from Part A (938 mg, 2.51 mmol) was stirred for 20 hours at ambient temperature in the presence of potassium hydroxide (940 mg, 17 mmol), ethanol (15 mL), and water (5 mL). The mixture was diluted with water (20 mL) and acidified using concentrated HCl to approximately pH 4. The product was extracted using chloroform (2 X 100 mL), and the combined organic layers were dried using anhydrous magnesium sulfate. Concentration afforded carboxylic acid (768 mg, 89%), which was carried on to the next step.

Part C: To a solution of the acid from Part B (764 mg, 2.2 mmol) dissolved in acetonitrile (15 mL)

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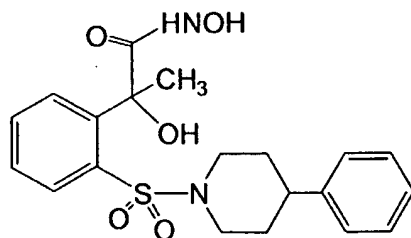
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was added O-tetrahydropyranyl hydroxylamine (351 mg, 3.0 mmol) and N-hydroxybenzotriazole (405 mg, 3.0 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (600 mg, 3 mmol).

5 The reaction was stirred for 16 hours and then concentrated. The residue was diluted with half-saturated brine (15 mL) and extracted with ethyl acetate (100 mL). The organic phase was dried using magnesium sulfate, concentrated, and the residue was  
10 purified by silica gel chromatography affording, on concentration, the desired THP-protected hydroxamate as a white foam (833 mg, 82%).

Part D: The THP-protected hydroxamate from Part C (833 mg, 1.8 mmol) was dissolved in absolute  
15 methanol (3 mL). Acetyl chloride (0.28 mL, 4 mmol) was added drop-wise. After 3 hours, the reaction was concentrated, and the residue was subjected to purification by chromatography, affording the title compound (430 mg, 66 %) as a white foam. Anal.  
20 calculated for  $C_{18}H_{20}N_2O_4S(H_2O)$ : C, 57.08; H, 5.81; N, 7.40. Found: C, 57.02; H, 5.61; N, 6.90.

Example 10: Preparation of N,2-Dihydroxy-2-methyl-2-[(4-phenyl-1-piperidinyl)-  
25 sulfonyl]benzeneacetamide



Part A: 2-Bromobenzenesulfonyl chloride (2.56  
30 g, 10 mmol) was added to a solution of 4-

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phenylpiperidine (1.61 g, 10 mmol), triethylamine (2.0 mL, 14 mmol), 4-dimethylaminopyridine (75 mg), and acetonitrile (20 mL). After 24 hours, water (100 mL) was added. The mixture was extracted with ethyl acetate (100 mL, then 50 mL). The combined organic layers were dried over magnesium sulfate, filtered through silica, and concentrated to afford the bromo sulfonamide as a white solid (3.47 g, 96%).

Part B: The bromo sulfonamide (359 mg, 1 mmol) was dissolved in dry tetrahydrofuran (2 mL) and cooled to minus seventy-eight degrees. *t*-Butyllithium (0.68 mL, 1.7 M in pentane) was added drop-wise and the anion was permitted to form over 15 minutes. Ethyl pyruvate (0.11 mL, 1.15 mmol) was added. The cooling bath was removed. When the reaction reached ambient temperature, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over magnesium sulfate, filtered through silica, concentrated, and chromatographed to afford the desired hydroxy ester as a glass (163 mg 40 %).

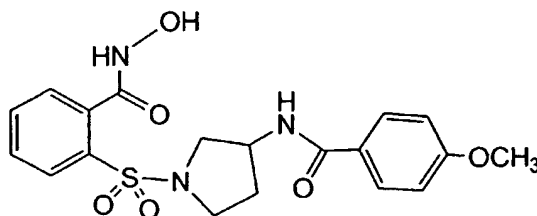
Part C: The hydroxy ester from Part B (134 mg, 0.33 mmol) was stirred in the presence of potassium hydroxide (134 mg, 2.4 mmol) in ethanol (1 mL) and water (1 mL). After 4 hours the mixture was heated at 50 degrees Celsius for one hour, then cooled, neutralized with dilute hydrochloric acid, concentrated, and azeotroped to dryness with acetonitrile to afford the crude hydroxy acid, which was used directly as is. The hydroxy acid was diluted with acetonitrile (1 mL). *O*-Tetrahydropyranylmethylhydroxylamine (117 mg, 1.0 mmol) and *N*-hydroxybenzotriazole (135 mg, 1.0 mmol) were added,

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followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (191 mg, 1 mmol). The reaction was stirred overnight (about 18 hours), then diluted with water (10 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over ethyl acetate, concentrated and chromatographed to afford the THP-protected hydroxamate as a glass (80 mg, 48%).

Part D: The THP-protected hydroxamate from Part C (80 mg) was diluted with absolute methanol (4 mL), and toluenesulfonic acid (6 mg) was added. After 3 hours, the reaction mixture was concentrated, and the residue was chromatographed using 1:1 hexane:ethyl acetate 1%  $\text{NH}_4\text{OH}$ . The title compound was isolated as a white foam (40 mg, 60%). Analysis calculated for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5\text{S}(1.33 \text{ H}_2\text{O})$ : C, 53.75; H, 5.90; N, 6.27. Found: C, 53.80; H, 5.65; N, 5.84.

Example 11: Preparation of N-Hydroxy-2-[[3-[(4-methoxybenzoyl)amino]-1-pyrrolidinyl]-sulfonyl]benzamide



Part A: 3-Aminopyrrolidine (636 mg, 4 mmol), triethylamine (2.7 mL, 20 mmol), and 4-(dimethylamino)pyridine (75 mg) were suspended in acetonitrile. After 10 minutes, the reaction was chilled to zero degrees Celsius. 4-Methoxybenzoyl chloride (0.54 mL, 4 mmol) was added, drop-wise.

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After 30 minutes, 2-carboethoxybenzenesulfonyl chloride (0.996 g, 4.0 mmol) was introduced, drop-wise, by syringe. The mixture was stirred at zero Celsius for 1 hour, then at ambient temperature for 2  
5 hours. Water was added (50 mL). The mixture was extracted using ethyl acetate (2 X 50 mL). The organic layer was dried over magnesium sulfate, filtered through silica, and concentrated. The residue was purified using silica gel chromatography  
10 using 1:1 ethyl acetate:hexane to ethyl acetate as eluant. The desired amide sulfonamide was isolated as a foam (282 mg, 16%).

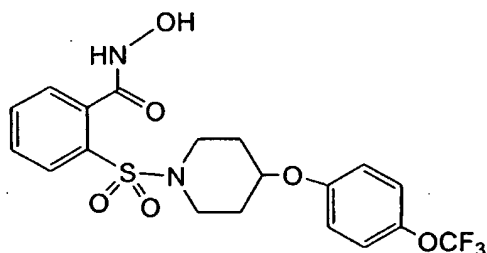
Part B: The amide sulfonamide from Part A (272 mg, 0.63 mmol) was combined with potassium hydroxide  
15 (156 mg, 2.8 mmol), ethanol (3 mL), and water (2 mL) and was brought to reflux. After 40 minutes, the reaction was permitted to cool. Acetic acid (0.1 mL) and absolute ethanol (20 mL) were added: Concentration followed by chromatography (9:1 ethyl  
20 acetate:methanol to methanol; 20 g silica gel) afforded the desired acid as a crystalline solid (229 mg, 96%). The acid (229 mg, 0.57 mmol) was dissolved in acetonitrile (1 mL). O-Tetrahydropyranyl hydroxylamine (117 mg, 1.0 mmol) and N-  
25 hydroxybenzotriazole (135 mg, 1.0 mmol) were added, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (191 mg, 1 mmol). The mixture was stirred at ambient temperature overnight (about 18 hours), then concentrated and  
30 chromatographed (ethyl acetate to 9:1 ethyl acetate:methanol), affording the THP-protected hydroxamate as a white crystalline solid (98 mg, 33%).



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Part C: The THP-protected hydroxamate (76 mg, 0.15 mmol) was dissolved in methanol (2 mL). Acetyl chloride (0.01 mL, 1 mmol) was added. After 30 minutes, the solution was concentrated, and then azeotroped with chloroform/acetonitrile affording the title compound as a solid (65 mg, quantitative.). MS (EI)  $MH^+$ : calculated for  $C_{19}H_{21}N_3O_6S$ : 420, found 420.

Example 12: Preparation of N-Hydroxy-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]benzamide



Part A: Diethyl azodicarboxylate (4.11 g, 23.6 mmol) was added at ambient temperature under an atmosphere of nitrogen to a mixture of N-(tert-butyloxycarbonyl)-4-piperidinol (4.31 g, 21.4 mmol) (Wells, Kenneth M.; et al; *Tetrahedron Lett.*, 1996, 37, 6439-6442), 4-trifluoromethoxyphenol (4.20 g, 23.6 mmol) and triphenylphosphine (6.19 g, 23.6 mmol) in THF (200 mL). After 1.5 hours, the reaction mixture was concentrated. The residue was diluted with ethyl ether, filtered, and purified by chromatography (on silica, methyl tert-butyl ether/hexane) to afford the impure BOC-amine as an off-white solid (5.23 g). To the off-white solid cooled to zero degrees Celsius under an atmosphere of nitrogen was added a solution of 4 N HCl in dioxane

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(36.1 mL, 145 mmol). After two hours, the reaction mixture was concentrated and diluted with ethyl ether to give a white solid. The white solid was diluted with H<sub>2</sub>O (15 mL) and a solution of NaHCO<sub>3</sub> (1.68 g, 20.0 mmol) in water (10 mL) was added. The precipitate was extracted into ethyl ether. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give the amine as a white solid (1.93 g, 34%); MS MH<sup>+</sup> calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>2</sub>F<sub>3</sub>:262, found 262.

Part B: A solution of the amine of Part A (1.90 g, 7.28 mmol), ethyl 2-chlorosulfonylbenzoate (1.70, 6.85 mmol), triethylamine (1.15 mL, 8.22 mmol), and 4-dimethylaminopyridine (10 mg) in acetonitrile (20 mL) was stirred under an atmosphere of nitrogen at ambient temperature for 18 hours. After concentrating the solution, the residue was diluted with H<sub>2</sub>O and extracted into ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine; and then dried over MgSO<sub>4</sub> and concentrated to a yellow oil. Chromatography (on silica, ethyl acetate/hexane) provided the sulfonamide as a white solid (1.59 g, 51%); MS MH<sup>+</sup> calculated for C<sub>21</sub>H<sub>22</sub>NO<sub>6</sub>F<sub>3</sub>S:474, found 474.

Part C: A solution of the sulfonamide of Part B (1.45 g, 3.17 mmol) and potassium hydroxide (1.77 g, 31.7 mmol) in a mixture of MeOH (30 mL), H<sub>2</sub>O (10 mL), and THF (10 mL) was heated at reflux for 1.5 hours. After the solution was concentrated *in vacuo*, the residue was triturated with ethyl ether, dissolved into H<sub>2</sub>O, acidified with concentrated HCl, and extracted into ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated

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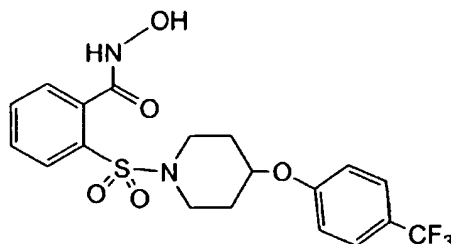
in vacuo to provide the acid as a clear oil (1.04 g, 74%); Anal. calculated for  $C_{19}H_{18}NO_6F_3S$ : C, 51.23; H, 4.07; N, 3.14; S, 7.20. Found: C, 51.34; H, 3.78; N, 3.15; S, 7.30.

5       Part D: A solution of the acid of Part C (0.97 g, 2.18 mmol), N-hydroxybenzotriazole (0.89 g, 6.50 mmol), 4-methylmorpholine (0.71 mL, 6.50 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.51 g, 4.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.25 g, 6.50 mmol)  
10       in DMF (19 mL) was stirred at ambient temperature under a nitrogen atmosphere for 20 hours. The mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The organic  
15       layer was washed with 1.0 N  $KHSO_4$ , saturated  $NaHCO_3$ ,  $H_2O$ , and brine; and then dried over  $MgSO_4$  and concentrated in vacuo to afford the THP-protected hydroxamate as a white solid (1.05 g, 88%): Anal. calculated. for  $C_{24}H_{27}N_2O_7F_3S$ : C, 52.94; H, 5.00; N,  
20       5.14; S, 5.89. Found: C, 52.80; H, 4.84; N, 5.23; S, 6.14.

      Part E: The THP-protected hydroxamate of Part D (1.01 g, 1.86 mmol) was dissolved in methanol (10 mL). Acetyl chloride (0.36 mL, 5.0 mmol) was added. After  
25       1 hour, the solution was concentrated, and the residue was subjected to chromatography (1:1 hexane:ethyl acetate; 1%  $NH_4OH$  to ethyl acetate; 1%  $NH_4OH$ ) affording the title compound as foam (643 mg, 75%). Anal. calculated for  $C_{19}H_{19}F_3N_2O_6S$ : C,  
30       49.56; H, 4.13; N, 6.09. Found: C, 49.27; H, 3.72; N, 5.87.

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Example 13: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide



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Part A: A solution of N-(tert-butyloxy-carbonyl)-4-piperidinol (5.00 g, 2.48 mmol), 4-fluorobenzo-trifluoride (3.46 mL, 2.73 mmol), and cesium carbonate (12.1 g, 3.72 mmol) in DMF (60 mL) was heated at 120 degrees Celsius under an atmosphere of nitrogen for 2 days. The mixture was concentrated, diluted with H<sub>2</sub>O, and extracted with ethyl acetate. The organic layer was washed with H<sub>2</sub>O and brine, dried with MgSO<sub>4</sub>, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexane) provided the BOC-aminoether as a white solid (6.97 g, 81%); Anal. calculated. for C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub>F<sub>3</sub>: C, 59.12; H, 6.42; N, 4.06. Found: C, 59.29; H, 6.47; N, 3.99.

Part B: A solution of the BOC-aminoether of Part A (4.00 g, 11.6 mmol) and p-toluenesulfonic acid (6.61 g, 34.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at ambient temperature under an atmosphere of nitrogen was stirred for 3 hours and then concentrated in vacuo. The residue was partitioned between aqueous NaHCO<sub>3</sub> and ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and concentrated to provide the free amine as a clear, yellow oil (1.57 g, 55%); MS MH<sup>+</sup> calculated. for C<sub>12</sub>H<sub>14</sub>NOF<sub>3</sub>: 246, found 246.

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Part C: A solution of the amine of Part B (1.57 g, 6.40 mmol), ethyl 2-chlorosulfonylbenzoate (1.57 g, 6.03 mmol), triethylamine (1.00 mL, 7.24 mmol), and 4-dimethylaminopyridine (10 mg) in acetonitrile (20 mL) was stirred under an atmosphere of nitrogen at ambient temperature for around 1.5 hours. After concentrating the solution, the residue was diluted with H<sub>2</sub>O and extracted into ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine; and then dried over MgSO<sub>4</sub> and concentrated to provided the sulfonamide as a clear, yellow oil (2.52 g, 92%); MS MH<sup>+</sup> calculated for C<sub>21</sub>H<sub>22</sub>NO<sub>5</sub>F<sub>3</sub>S: 458, found 458.

Part D: A solution of the sulfonamide of Part C (2.50 g, 5.46 mmol) and potassium hydroxide (3.06 g, 54.6 mmol) in a mixture of MeOH (49 mL) and H<sub>2</sub>O (24 mL) was heated at reflux for 4 hours. After the solution was concentrated in vacuo, the residue was triturated with ethyl ether, dissolved into H<sub>2</sub>O, acidified with concentrated HCl, and extracted into ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, H<sub>2</sub>O, and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo to provide the acid as an oil (2.17 g, 93%); MS MH<sup>+</sup> calculated for C<sub>19</sub>H<sub>18</sub>NO<sub>5</sub>F<sub>3</sub>S: 430, found 430.

Part E: A solution of the acid of Part D (2.10 g, 4.89 mmol), N-hydroxybenzotriazole (1.97 g, 14.6 mmol), 4-methylmorpholine (1.61 mL, 14.6 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.15 g, 9.79 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.80 g, 14.6 mmol) in DMF (43 mL) was stirred at ambient temperature under a nitrogen atmosphere for about 18 hours. The

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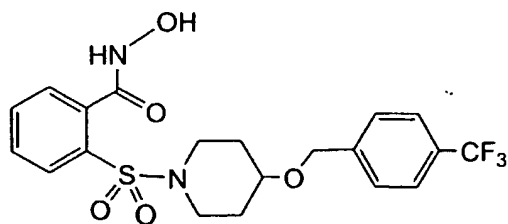
mixture was concentrated *in vacuo*, diluted with water, and extracted into ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, H<sub>2</sub>O, and brine, and then dried over MgSO<sub>4</sub> and concentrated *in vacuo*.

- 5 Chromatography (on silica, ethanol/CHCl<sub>3</sub>) provided the THP-protected hydroxamate as a white solid (2.09 g, 81%): MS MH<sup>+</sup> calculated for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>S: 529, found 529.

- Part F: To a solution of the THP-protected  
10 hydroxamate of Part C (1.80 g, 3.41 mmol) in methanol (24 mL) was added acetyl chloride (0.73 mL, 10.2 mmol) and the solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hours. The solution was concentrated *in vacuo* and  
15 chromatography (on silica, MeOH/CHCl<sub>3</sub>) provided the title compound as an off white solid (1.18 g, 78%):  
Anal. calculated. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub>F<sub>3</sub>S·0.2%<sub>2</sub>O: C, 50.94; H, 4.36; N, 6.25; S, 7.16. Found: C, 50.88; H, 4.31; N, 6.20; S, 7.43. MS MH<sup>+</sup> calculated. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub>F<sub>3</sub>S:  
20 445, found 445.

Example 14: Preparation of N-hydroxy-2-[[4-[[4-(trifluoromethyl)phenyl]methoxy]-1-piperidinyl]sulfonyl]benzamide

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- Part A: A solution of 4-(trifluoromethyl)benzyl  
bromide (2.00 mL, 12.9 mmol) in THF (6 mL) was added  
30 drop-wise under an atmosphere of nitrogen to a -52

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degrees Celsius mixture of N-(tert-butyloxycarbonyl)-4-piperidinol (2.85, 14.9 mmol) and 60% sodium hydride (0.600 g, 14.9 mmol) in THF (15 mL) and then stirred at ambient temperature for about 20 hours.

5 The reaction mixture was quenched with a saturated  $\text{NH}_4\text{Cl}$  solution, concentrated *in vacuo*, diluted with  $\text{H}_2\text{O}$ , and extracted with ethyl acetate. The organic layer was washed with 1.0 N  $\text{HCl}$ , a saturated  $\text{NaHCO}_3$  solution,  $\text{H}_2\text{O}$ , and brine; and then dried over  $\text{MgSO}_4$

10 and concentrated *in vacuo* to provide the BOC-aminoether as an off white solid (3.35 g, 72%); MS  $\text{MH}^+$  calculated for  $\text{C}_{18}\text{H}_{24}\text{NO}_3\text{F}_3$ : 360, found 360.

Part B: A zero degrees Celsius solution of the BOC-aminoether of Part A (3.35 g, 9.32 mmol) in ethyl acetate (40 mL) was saturated with  $\text{HCl}$  (gas) and the stirred at ambient temperature for 1 hour. After concentrating *in vacuo* and triturating with ethyl ether, the crude free base was partitioned between aqueous  $\text{NaHCO}_3$  and ethyl ether. The organic layer was

15 washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to provide the amine as a clear, yellow oil (2.11 g, 87%), which had a proton NMR spectrum consistent for the desired product.

Part C: A solution of the amine of Part B (2.11 g, 8.14 mmol), ethyl 2-chlorosulfonylbenzoate (2.65 g, 10.7 mmol), triethylamine (1.75 mL, 12.6 mmol), and 4-dimethylaminopyridine (50 mg) in acetonitrile (25 mL) was stirred under an atmosphere of nitrogen at ambient temperature for about 18 hours. After

25 concentrating the solution, the residue was diluted with 1.0 N  $\text{KHSO}_4$  and extracted into ethyl acetate. The organic layer was washed with 1.0 N  $\text{KHSO}_4$ , saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , and brine, and then dried over

30

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MgSO<sub>4</sub> and concentrated to a yellow oil.

Chromatography (on silica, ethyl acetate/hexane) provided the sulfonamide as a clear oil (2.48 g, 65%); MS MH<sup>+</sup> calculated for C<sub>22</sub>H<sub>24</sub>NO<sub>5</sub>F<sub>3</sub>S: 472, found 5 472.

Part D: A solution of the sulfonamide of Part C (2.10 g, 4.45 mmol) and potassium hydroxide (2.49 g, 44.5 mmol) in a mixture of MeOH (40 mL), H<sub>2</sub>O (20 mL), and THF (4 mL) was heated at reflux for 1.5 hours.

10 After the solution was concentrated *in vacuo*, the residue was triturated with ethyl ether, dissolved into H<sub>2</sub>O, acidified with concentrated HCl, and extracted into ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, H<sub>2</sub>O, and brine, dried over 15 MgSO<sub>4</sub>, and concentrated *in vacuo* to provide the acid as a white solid (2.08 g, 1.06%); Anal. Calculated for C<sub>20</sub>H<sub>20</sub>NO<sub>5</sub>F<sub>3</sub>S: C, 54.17; H, 4.55; N, 3.16; S, 7.23. Found: C, 54.29; H, 4.68; N, 3.11; S, 7.19.

Part E: A solution of the acid of Part D (2.00 20 g, 4.51 mmol), N-hydroxybenzotriazole (1.83 g, 13.5 mmol), 4-methylmorpholine (1.48 mL, 13.5 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.06 g, 9.02 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.59 g, 13.5 mmol) 25 in DMF (40 mL) was stirred at ambient temperature under a nitrogen atmosphere for about 20 hours. The mixture was concentrated *in vacuo*, diluted with water, and extracted into ethyl acetate. The organic layer was washed with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and 30 brine, and then dried over MgSO<sub>4</sub> and concentrated *in vacuo* to provide the THP-protected hydroxamate as a white solid (2.01 g, 82%): Anal. calculated. for



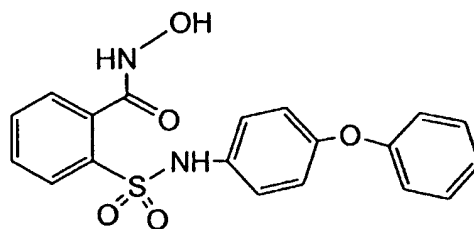
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$C_{25}H_{29}N_2O_6F_3S$ : C, 55.34; H, 5.39; N, 5.16; S, 5.91.

Found: C, 55.36; H, 5.63; N, 5.20; S, 6.12.

Part F: To a solution of the THP-protected hydroxamate of Part E (2.00 g, 3.69 mmol) in methanol (25.9 mL) was added acetyl chloride (0.78 mL, 11.1 mmol), and the solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hours. The solution was concentrated *in vacuo* and chromatography (on silica, MeOH/ $CHCl_3$ ) provided the title compound as an off-white solid (1.07 g, 63%):  
Anal. calculated. for  $C_{20}H_{21}N_2O_5F_3S$ : C, 52.40; H, 4.62; N, 6.11; S, 6.99. Found: C, 52.53; H, 4.74; N, 6.25; S, 7.16. MS  $MH^+$  calculated. for  $C_{20}H_{21}N_2O_5SF_3$ : 459, found 459.

Example 15: Preparation of N-Hydroxy-2-[[(4-phenoxyphenyl)aminosulfonyl]]benzamide



20

Part A: A solution of 4-phenoxyaniline (3.43 g, 18.5 mmol), ethyl 2-chlorosulfonylbenzoate (4.25 g, 17.1 mmol), triethylamine (2.81 mL, 20.1 mmol), and 4-dimethylaminopyridine (50 mg) in acetonitrile (40 mL) was stirred under an atmosphere of nitrogen at ambient temperature for about 18 hours. After concentrating the solution, the residue was diluted with 1.0 N  $KHSO_4$  and extracted into ethyl acetate. The organic layer was washed with 1.0 N  $KHSO_4$ ,  $H_2O$ , and brine, and then dried over  $MgSO_4$  and concentrated

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in vacuo. Chromatography (on silica, ethyl acetate/hexane) provided the sulfonamide as a tan solid (4.94 g, 73%); Anal. calculated. for  $C_{21}H_{19}NO_5S$ : C, 63.46; H, 4.82; N, 3.52; S, 8.07. Found: C, 63.36; H, 4.78; N, 3.45; S, 8.31. MS  $M^+$  calculated for  $C_{21}H_{19}NO_5S$ : 397, found 397.

Part B: A solution of the sulfonamide of Part A (3.00 g, 7.55 mmol) and potassium hydroxide (4.23 g, 75.5 mmol) in a mixture of MeOH (68 mL), THF (8 mL), and  $H_2O$  (33 mL) was heated at reflux for 2 hours. After the solution was concentrated in vacuo, the residue was triturated with ethyl ether, dissolved into  $H_2O$ , acidified with concentrated HCl, and extracted into ethyl acetate. The organic layer was washed with 1.0 N HCl,  $H_2O$ , and brine, dried over  $MgSO_4$ , and concentrated in vacuo to provide the acid as a tan solid (2.31 g, 83%); Anal. calculated. for  $C_{19}H_{15}NO_5S$ : C, 61.78; H, 4.09; N, 3.79; S, 8.68. Found: C, 61.66; H, 4.22; N, 3.73; S, 8.70. MS  $M^+$  calculated for  $C_{19}H_{15}NO_5S$ : 369, found 369.

Part C: A solution of the acid of Part B (2.30 g, 6.23 mmol), N-hydroxybenzotriazole (2.52 g, 18.6 mmol), 4-methylmorpholine (2.04 mL, 18.6 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.46 g, 12.5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.57 g, 18.6 mmol) in DMF (55 mL) was stirred at ambient temperature under a nitrogen atmosphere for about 18 hours. The mixture was diluted with water, and extracted into ethyl acetate. The organic layer was washed with saturated  $NaHCO_3$ ,  $H_2O$ , and brine, and then dried over  $MgSO_4$  and concentrated in vacuo to provide the saccharin compound as a white solid (2.13 g, 97%):

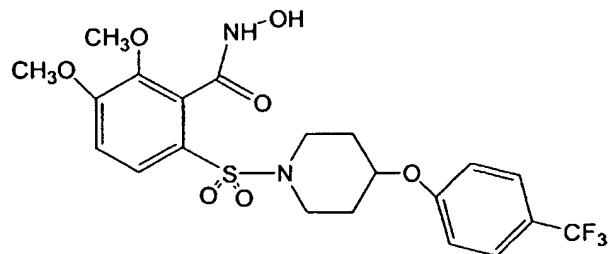
-237-

Anal. calculated. for  $C_{19}H_{13}NO_4S$ : C, 64.95; H, 3.73; N, 3.99; S, 9.13. Found: C, 64.98; H, 3.82; N, 4.17; S, 9.07. MS  $MH^+$  calculated for  $C_{19}H_{13}NO_4S$ : 352, found 352.

- 5        Part D: A solution of the saccharin of Part C (0.500 g, 1.42 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.183 g, 1.56 mmol) in dioxane (2 mL) under an atmosphere of nitrogen was stirred for 6 days at ambient temperature and 1 day at 50 degrees  
10        Celsius. The solution was concentrated and chromatography provided the THP-protected hydroxamate as a white solid (0.285 g, 43%); MS  $MH^+$  calculated for  $C_{24}H_{24}N_2O_6S$ : 469, found 469.

- Part E: To a solution of the THP-protected  
15        hydroxamate of Part D (0.275 g, 0.587 mmol) in methanol (5 mL) was added acetyl chloride (0.150 mL, 2.13 mmol) and the solution was stirred at ambient temperature under a nitrogen atmosphere for 2 hours. The solution was concentrated in vacuo and  
20        chromatography (on silica, MeOH/ $CHCl_3$ ) provided the title compound as an off-white solid (1.18 g, 78%). The proton NMR was consistent for the desired product.

- 25        Example 16: Preparation of N-Hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide



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Part A: The piperidine from Example 13, Part B (as the hydrochloride) (1.12 g, 4.0 mmol) was dissolved in a mixture of acetonitrile (6 ml), triethylamine (1.3 mL, 9.0 mmol), and N,N-dimethylaminopyridine (80 mg). 3,4-Dimethoxybenzenesulfonyl chloride (947 mg, 4.0 mmol) was added, and the mixture was stirred at ambient temperature for 6 hours. The reaction mixture was concentrated, and the residue was extracted with ethyl acetate (100, then 25 mL). The combined organic layers were dried over magnesium sulfate, filtered through silica, and concentrated to afford the desired sulfonamide as a white solid (1.05 g, 59%)

Part B: The sulfonamide from Part A (1.05 g, 2.38 mmol) was dissolved in tetrahydrofuran (20 mL) and was cooled to zero degrees Celsius. t-Butyllithium (1.7 M in pentane, 2.8 mL) was added drop-wise. Fifteen minutes after complete addition of the base, the solution was rapidly saturated with dry carbon dioxide gas. After an additional 15 minutes, the solution was acidified with a minimum of concentrated hydrogen chloride. The reaction mixture was concentrated, azeotroped with absolute ethanol, and the residue was subjected to silica gel chromatography, using 8:1 ethyl acetate:methanol, affording the desired acid as a glass (279 mg, 24%).

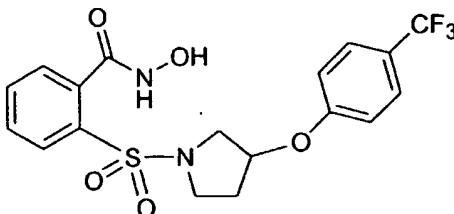
Part C: The acid from Part B (231 mg, 0.47 mmol) was dissolved in methylene chloride (4 mL). N,N-Dimethylformamide (2 drops) was added, followed by oxalyl chloride (0.35 mL, 4 mmol). The reaction was stirred for 1.5 hours at ambient temperature, during which time gas was evolved. The reaction

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mixture was concentrated, and dried *in vacuo*,  
affording crude acid chloride, which was used as is.  
To the acid chloride was added a solution of O-  
tetrahydropyranylhydroxylamine (234 mg, 2.0 mmol) and  
5 pyridine (0.5 mL, 6.0 mmol) in acetonitrile (2-3 mL).  
The reaction was stirred at ambient temperature for  
16 hours, then was diluted with water (3 mL). The  
mixture was extracted with ethyl acetate (100 mL,  
then 50 mL). The combined organic layers were dried  
10 over magnesium sulfate, filtered through a silica  
pad, and concentrated, affording 376 mg of crude THP-  
protected hydroxamate. The THP-protected hydroxamate  
was used directly without purification and was  
diluted with absolute methanol (10 mL). Acetyl  
15 chloride (0.36 mL, 5.0 mmol) was added, drop-wise.  
After 2.5 hours, the mixture was concentrated and the  
residue was chromatographed (ethyl acetate:1%  $\text{NH}_4\text{OH}$ ).  
The desired hydroxamate was obtained as a glass (121  
mg, 51% from acid). MS  $\text{MH}^+$  calculated for  $\text{C}_{21}\text{H}_{23}$   
20  $\text{F}_3\text{N}_2\text{O}_7\text{S}$ : 505, found 505.

Example 17: Preparation of N-Hydroxy-2-[[3-[4-  
(trifluoromethyl)phenoxy]-1-  
pyrrolidinylsulfonylbenzamide

25



Part A: Diethyl azodicarboxylate (2.03 mL, 12.9  
mmol) was added under an atmosphere of nitrogen to a

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solution of 1-(tert-butoxycarbonyl)-3-hydroxypyrrrolidine (2.31 g, 12.3 mmol), p-trifluoromethylphenol (2.09 g, 12.9 mmol), and triphenylphosphine (3.38 g, 12.9 mmol) in anhydrous THF (40 mL) at ambient temperature. After stirring for 2 hours, the reaction was concentrated *in vacuo*. The residue was diluted with ether, filtered through a silica gel bed, concentrated, and purified by flash chromatography (on silica, ethyl acetate/hexane) to afford the BOC-protected amine as a white solid (1.85 g, 45%); Anal. Calculated for  $C_{16}H_{20}NO_3F_3$ : C, 58.00; H, 6.08; N, 4.23. Found: C, 57.86; H, 6.17; N, 3.92.

Part B: To the BOC-protected amine of Part A (1.75 g, 5.28 mmol) was added a solution of 4 N HCl in dioxane (13.2 mL, 52.8 mmol). After 1 hour, the reaction mixture was concentrated, diluted with ethyl ether, and concentrated to give an oil. The oil was dissolved in water and saturated  $NaHCO_3$  solution was added until the pH value was 8. The mixture was extracted with ethyl acetate. The organic layer was washed with  $H_2O$  and brine, dried over  $MgSO_4$ , and concentrated *in vacuo* to give the amine as a clear, yellow oil (0.75 g, 61%); MS  $MH^+$  calculated for  $C_{11}H_{12}NOF_3$ : 231, found 232.

Part C: A solution of the amine of Part B (0.680 g, 2.94 mmol), ethyl 2-chlorosulfonylbenzoate (0.688, 2.77 mmol), triethylamine (0.46 mL, 3.3 mmol), and 4-dimethylaminopyridine (10 mg) in acetonitrile (10 mL) was stirred under an atmosphere of nitrogen at ambient temperature for 18 hours. After concentrating *in vacuo*, the residue was diluted with  $H_2O$  and extracted with ethyl acetate. The organic layer was washed with 1.0 N  $KHSO_4$ , saturated

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NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine, dried over MgSO<sub>4</sub> and concentrated to a yellow oil. Chromatography (on silica, ethyl acetate/hexane) provided the sulfonamide as a clear, colorless oil (0.95 g, 76%);  
5 MS MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>20</sub>NO<sub>5</sub>F<sub>3</sub>S: 443, found 444. Anal. Calculated for C<sub>20</sub>H<sub>20</sub>NO<sub>5</sub>F<sub>3</sub>S: C, 54.17; H, 4.55; N, 3.16; S, 7.23. Found: C, 53.82; H, 4.35; N, 3.13.

Part D: A solution of the sulfonamide of Part C (0.85 g, 1.9 mmol) and potassium hydroxide (1.07 g,  
10 19.2 mmol) in a mixture of MeOH (17 mL) and H<sub>2</sub>O (8 mL) was heated at reflux for 4 hours. After the solution was concentrated *in vacuo*, the residue was dissolved into H<sub>2</sub>O, acidified with concentrated HCl, and extracted into ethyl acetate. The organic layer was  
15 washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to provide the acid as a clear, colorless wax (0.74 g, 93%); MS MH<sup>+</sup> calculated for C<sub>18</sub>H<sub>16</sub>NO<sub>5</sub>F<sub>3</sub>S: 415, found 416.

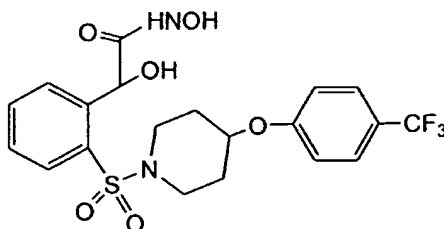
Part E: A solution of the acid of Part D (0.690  
20 g, 1.56 mmol), N-hydroxybenzotriazole (0.629 g, 4.65 mmol), 4-methylmorpholine (0.51 mL, 4.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.340 g, 2.90 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.891 g, 4.65 mmol)  
25 in DMF (13 mL) was stirred at ambient temperature under a nitrogen atmosphere for 3 days. The mixture was concentrated *in vacuo*, diluted with 1.0 N KHSO<sub>4</sub>, and extracted with ethyl acetate. The organic layer was washed with 1.0 N KHSO<sub>4</sub>, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O,  
30 and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. Chromatography on silica, with ethyl acetate/hexane as eluant afford the THP-protected hydroxamate as a white foam (0.575 g, 71.6%): Anal.

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calculated. for  $C_{23}H_{25}N_2O_6F_3S$ : C, 53.69; H, 4.90; N, 5.44; S, 6.23. Found: C, 53.48; H, 4.95; N, 5.37; S, 6.35.

Part F: To a solution of the THP-protected  
5 hydroxamate of Part E (0.500 g, 0.972 mmol) in methanol (6 mL) was added acetyl chloride (0.24 mL, 3.5 mmol) and the solution was stirred at ambient temperature under a nitrogen atmosphere for 4.5 hours. The solution was concentrated *in vacuo* and  
10 chromatography (on silica, MeOH/ $CHCl_3$ ) provided the title compound as a white solid (0.325 g, 77.8%): MS  $MH^+$  calculated. for  $C_{18}H_{17}N_2O_5SF_3$ : 430, found 431.

15 Example 18: Preparation of N- $\alpha$ -Dihydroxy-2-  
[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzeneacetamide  
piperidinyl]sulfonyl]benzeneacetamide



20 Part A: A mixture of 4-[(4-trifluoromethyl)-phenoxy]piperidine hydrochloride (the hydrochloride from the product of Example 13, Part B (2.50 g, 8.87 mmol), 2-bromobenenesulfonyl chloride (2.16 g, 8.45 mmol), triethylamine (2.51 mL, 18.0 mmol), and 4-  
25 (dimethylamino)pyridine (20 mg) in acetonitrile (25 mL) was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours, concentrated *in vacuo*, and partitioned between  $H_2O$  and ethyl acetate. The organic layer was washed with 1.0 N  $KHSO_4$ ,  
30 saturated  $NaHCO_3$ ,  $H_2O$ , and brine, dried over  $MgSO_4$ ,



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and concentrated *in vacuo*. The oil was purified by chromatography (on silica, ethyl acetate/hexane) to provide the bromide as a clear oil (3.38 g, 82.8%): MS+ calculated. for  $C_{18}H_{17}NO_3SF_3Br$  464, found 464.

5           Part B: To a -78 degree Celsius solution of the sulfonamide from Part A (3.68 g, 7.93 mmol) in anhydrous THF (40 mL) under an atmosphere of nitrogen was added 1.7 M tert-butyl lithium (9.35 mL, 15.9 mmol). The reaction was maintained at -78 degrees  
10 Celsius for 1 hour, warmed up to -30 degrees Celsius, and then cooled down to -78 degrees Celsius. A 50% ethyl glyoxalate solution in toluene was added dropwise while maintaining the reaction mixture at a temperature below -50 degrees Celsius. The solution  
15 was warmed up slowly to ambient temperature, stirred 2 days at ambient temperature, poured into a saturated  $NH_4Cl$  solution, diluted with  $H_2O$ , and extracted with ethyl acetate. The organic layer was washed with  $H_2O$  and brine, dried over  $MgSO_4$ , and  
20 concentrated *in vacuo*. Chromatography on silica, with ethyl acetate/hexane as eluant provided the ester as a yellow oil (1.55 g, 40%); Anal. calculated. for  $C_{22}H_{24}NO_6F_3S$ : C, 54.20; H, 4.96; N, 2.87. Found: C, 54.18; H, 4.72; N, 2.77. MS  $MH^+$   
25 calculated for  $C_{22}H_{24}NO_6F_3S$ : 487, found 488.

          Part C: A solution of the ester of Part B (1.35 g, 2.77 mmol) and potassium hydroxide (1.55 g, 27.7 mmol) in a mixture of MeOH (24.5 mL) and  $H_2O$  (14.7 mL) was stirred at ambient temperature for 1 hour. The  
30 solution was concentrated *in vacuo*, dissolved into a mixture of  $H_2O$  and acetonitrile, acidified with concentrated HCl, and extracted with ethyl acetate. The organic layer was washed with 1.0 N  $KHSO_4$ ,  $H_2O$ ,

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and brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo to provide the acid as a wax (1.09 g, 85.8%); Anal. calculated. for  $\text{C}_{20}\text{H}_{20}\text{NO}_6\text{F}_3\text{S}$ : C, 52.29; H, 4.39; N, 3.05; S, 6.98. Found: C, 52.06; H, 4.41; N, 2.90; S, 7.11.

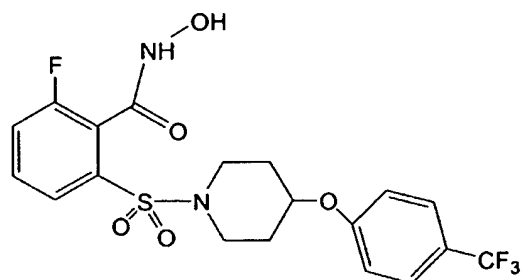
Part D: A solution of the acid of Part C (1.00 g, 2.18 mmol), N-hydroxybenzotriazole (0.876 g, 6.48 mmol), 4-methylmorpholine (0.712 mL, 6.48 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.474 g, 4.05 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.24 g, 6.48 mmol) in DMF (15 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18 hours. The mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The organic layer was washed with 1.0 N  $\text{KHSO}_4$ , saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. Chromatography on silica with ethyl acetate/hexane as eluant provided the THP-protected hydroxamate as a white solid (0.81 g, 66%); Anal. calculated. for  $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_7\text{F}_3\text{S}$ : C, 53.76; H, 5.23; N, 5.02; S, 5.74. Found: C, 53.73; H, 5.39; N, 4.85; S, 5.72.

Part E: A solution of the THP-protected hydroxamate of Part D (0.800 g, 1.43 mmol) and acetyl chloride (0.36 mL, 5.2 mmol) in methanol (15 mL) was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hours. The solution was concentrated in vacuo and purified by preparatory HPLC ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ) to provide the title compound as a white solid (0.310 g, 45%). Anal. calculated. for  $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_6\text{SF}_3 \cdot 0.2\% \text{H}_2\text{O}$ : C, 50.25; H, 4.51; N, 5.86; S, 6.71. Found: C, 50.18; H, 4.52; N, 5.82; S, 6.58

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Example 19: Preparation of 2-Flouro-N-hydroxy-6-  
[[4-[4-(trifluoromethyl)phenoxy]-1-  
piperidinyl]sulfonyl]benzamide

5



Part A: A solution of the piperidine from  
Example 13, Part B (as the hydrochloride) (2.0 g,  
10 6.72 mmol), 3-flouorobenzenesulphonyl chloride (1.19  
g, 6.11 mmol), triethylamine (2.13 mL, 15.3 mmol),  
and 4-dimethylaminopyridine (10 mg) in acetonitrile  
(10 mL) was stirred under an atmosphere of argon at  
ambient temperature for 18 hours. After  
15 concentrating the solution, the residue was diluted  
with H<sub>2</sub>O and extracted into ethyl acetate. The  
organic layer was washed with saturated NaHSO<sub>4</sub>, H<sub>2</sub>O,  
and brine; and dried over MgSO<sub>4</sub> and concentrated to an  
oil. Chromatography (on silica, 20% ethyl  
20 acetate/hexane) provided the sulfonamide as a viscous  
oil (2.35 g, 95%); MS H<sup>+</sup> calculated for  
C<sub>18</sub>H<sub>17</sub>NSO<sub>3</sub>F<sub>4</sub>:404, found 404.

Part B: t-Butyl lithium (3.5 mL, 5.96 mmol) was  
added to a solution of the sulfonamide of Part A (1.2  
25 g, 2.98 mmol) in dry THF (10 mL) at 0°C. The solution  
was stirred at this temperature for 15 minutes.  
Carbon dioxide was bubbled into the reaction mixture  
for 7 minutes at 0°C, and the mixture was stirred for  
0.5 hours. Water was added to the solution, the

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mixture was acidified to pH = 1.0 with 1 N HCl, and concentrated *in vacuo* to give an oil. Chromatography (on silica, 1% acetic acid/5% methanol/ethyl acetate) provided the acid as a white powder (0.970 mg, 73%).

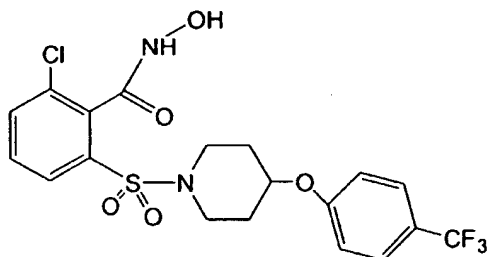
5 MS H<sup>+</sup> calculated for C<sub>19</sub>H<sub>16</sub>NSO<sub>5</sub>F<sub>4</sub>:448, found 448.

Part C: A solution of the acid of Part B (880 mg, 1.97 mmol), N-hydroxybenzotriazole (319 mg, 2.36 mmol), 4-methylmorpholine (0.649 mL, 5.91 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (346 mg, 2.95  
10 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (528 mg, 2.76 mmol) in DMF (10 mL) was stirred at ambient temperature under an argon atmosphere for 18 hours, followed by stirring at 60°C for 24 hours. The mixture was  
15 concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a solid. Chromatography on a C-18 reverse phase column, eluting with acetonitrile/water  
20 afforded the THP-protected hydroxamate as a white solid (240 mg, 30%).

Part D: To a solution of the THP-protected hydroxamate of Part C (230 mg, 0.422 mmol), in dioxane (5 mL) was added 4 N HCl (1 mL), and the  
25 solution was stirred at ambient temperature under argon atmosphere for 1 hour. The solution was concentrated *in vacuo* to give an oil. Chromatography on a C-18 reverse phase column, eluting with acetonitrile/water afforded the titled hydroxamate as  
30 a white foam (180 mg, 92%).

Example 20: Preparation of 2-Chloro-N-hydroxy-6-  
[[4-[4-(trifluoromethyl)phenoxy]-1-  
piperidinyl]sulfonyl]benzamide

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Part A: A solution of the amine of piperidine  
5 from Example 13, Part B (as the hydrochloride) (2.00  
g, 6.72 mmol), 3-chlorobenzenesulphonyl chloride  
(1.29 g, 6.11 mmol), triethylamine (2.2 mL, 15.3  
mmol), and 4-dimethylaminopyridine (10 mg) in  
acetonitrile (10 mL) was stirred under an atmosphere  
10 of argon at ambient temperature for 18 hours. After  
concentrating the solution, the residue was diluted  
with H<sub>2</sub>O and extracted into ethyl acetate. The  
organic layer was washed with saturated NaHSO<sub>4</sub>, H<sub>2</sub>O,  
and brine, and dried over MgSO<sub>4</sub> and concentrated to an  
15 oil. Chromatography (on silica, 20% ethyl  
acetate/hexane) provided the sulfonamide as a viscous  
oil (2.44 g, 95%); MS H<sup>+</sup> calculated for  
C<sub>18</sub>H<sub>17</sub>NSO<sub>3</sub>F<sub>3</sub>Cl:419, found 419.

Part B: t-Butyl lithium (3.4 mL, 5.7 mmol) was  
20 added to a solution of the sulfonamide of Part A (1.2  
g, 2.9 mmol) in dry THF (10 mL) at 0°C. The solution  
was stirred at this temperature for 15 minutes.  
Carbon dioxide was bubbled into the reaction mixture  
for 7 minutes at 0°C, then the reaction was stirred  
25 for 1.5 hours. Water was added to the solution,  
which was then acidified to pH = 1.0 with 1 N HCl,  
and then concentrated in vacuo to give an oil.  
Chromatography (on silica, 1% acetic acid/5%

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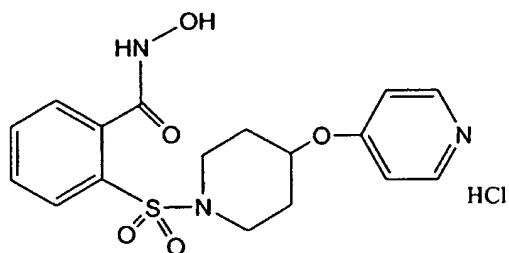
methanol/ethyl acetate) provided the acid as a white powder (320 mg, 24%).

Part C: Oxalyl chloride (0.154 mL) was added to a solution of the acid of Part B (410 mg, 0.88 mmol) in methylene chloride (4 mL) at ambient temperature and the solution was stirred under argon atmosphere for 1 hour. The solution was concentrated *in vacuo* to give the acid chloride. To the acid chloride in DMF (5 mL) was added 4-methylmorpholine (0.200 mL, 1.77 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (155 mg, 1.30 mmol) and the reaction was stirred at ambient temperature under an argon atmosphere for 4 hours. The mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give an oil. Chromatography on a C-18 reverse phase column, eluting with acetonitrile/water afforded the THP-protected hydroxamate as a white foam (260 mg, 52%).

Part D: To a solution of the THP-protected hydroxamate of Part C in dioxane was added 4 N HCl and the was solution stirred at ambient temperature under argon atmosphere for 1 hour. The solution was concentrated *in vacuo* to give a semi-solid. Chromatography (on silica, 60% ethyl acetate/hexane) provided the title compound.

Example 21: Preparation of N-Hydroxy-2-[[4-(4-pyridinyloxy)-1-piperidinyl]sulfonyl]-benzamide, monohydrochloride

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Part A: To a solution of N-BOC-4-hydroxypiperidine (3.00 g, 14.9 mmol) in  
5 dimethylsulfoxide (10 mL) are sequentially added 4-chloropyridine hydrochloride (2.35 g, 15.6 mmol) and potassium-t-butoxide (30.5 mL of a 1.0 M solution in tetrahydrofuran, 30.5 mmol). After 16 hours at  
10 ambient temperature, the reaction mixture is diluted with diethyl ether (100 mL) and washed with water (3X) and brine, and then dried over sodium sulfate. Concentration of the organic solution gives the  
desired 4-pyridyloxypiperidine (4.24 g, 100%) as a white solid. Analytical calculation for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C,  
15 64.73; H, 7.97; N, 10.06. Found: C, 64.48; H, 8.14; N, 9.82.

Part B: A solution of hydrogen chloride in 1,4-dioxane (20 mL of a 4 N solution, 80 mmol) is added  
to a solution of pyridyloxypiperidine of Part A (3.81  
20 g, 13.7 mmol) in 1,4-dioxane (28 mL) at ambient temperature. After one hour, the suspension is concentrated and the residue triturated with hot isopropanol. The resulting solid is dried at 50 degrees Celsius under vacuum to afford the desired piperidine  
25 hydrochloride salt as a white powder (3.03 g, 88%). Analytical calculation for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O.2HCl: C, 47.82; H, 6.42; N, 11.15. Found: C, 47.40; H, 6.64; N, 11.04.

-250-

Part C: The solid piperidine hydrochloride from Part B (450 mg, 1.79 mmol) is added to a solution of 2-carboxyethoxy-benzenesulfonyl chloride (580 mg, 2.33 mmol) in acetonitrile (5 mL), followed by the addition of neat triethylamine (0.95 mL, 7.16 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol). Additional acetonitrile (10 mL) is added, along with methylene chloride (3 mL) to aid in dissolution. After 16 hours at ambient temperature, water (100 mL) is added and the mixture is extracted twice with ethyl acetate. The combined organic extracts are washed successively with water (3X) and brine, and then dried over sodium sulfate. Concentration gives a residue (0.49 g) that is chromatographed on silica gel eluting with ethanol/ethyl acetate (4/96) to afford the desired aryl sulfonamide (462 mg, 66%) as a pale yellow foam. Analytical calculation for  $C_{19}H_{22}N_2O_5S \cdot \frac{1}{2}H_2O$ : C, 56.49; H, 5.86; N, 6.93. Found: C, 56.36; H, 5.88; N, 6.68.

Part D: Sodium hydroxide (10 equivalents) is added to a solution of the aryl sulfonamide of Part C in ethanol, water and tetrahydrofuran, and the solution is heated to 60 degrees Celsius for 24 hours. The solution is cooled and then diluted with water followed by 10% aqueous hydrochloric acid to bring the pH value to 3. The resulting solution is extracted with ethyl acetate. The organic extracts are combined and washed with water and brine, and dried over sodium sulfate to afford the desired carboxylic acid.

Part E: To a solution of the carboxylic acid of Part D in N,N-dimethylformamide are added 4-methylmorpholine (6.0 equivalents), N-



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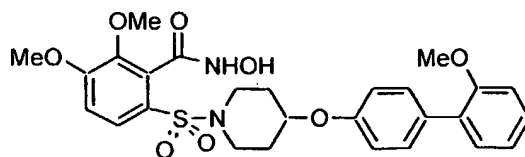
hydroxybenzotriazole (1.2 equivalents), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.3 equivalents), followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.3 equivalents). After stirring for 2 days at ambient temperature the solution is concentrated. Water is added and the mixture is extracted with ethyl acetate. The organic extracts are washed with water and brine, and dried over sodium sulfate.

Concentration affords a residue that is chromatographed on silica gel eluting with ethyl acetate/hexane (20/80 to 90/10) as eluate to afford the THP-protected hydroxamate derivative.

Part F: To a solution of the THP-protected hydroxamate of Part E in 1,4-dioxane is added 4 N HCl in 1,4-dioxane (10 equivalents), and the solution is permitted to stir at ambient temperature for 3 hours. Concentration gives a residue that is then triturated with diethyl ether to afford the title compound.

20

Example 22: Preparation of N-Hydroxy-2,3-dimethoxy-6-[[4-[(2'-methoxy[1,1'-biphenyl]-4-yl)-oxy-1-piperidinyl]sulfonyl]benzamide



25

Part A: To a solution of N-BOC-4-hydroxypiperidine (25 mmol, 5.0 g) in 1-methyl-2-pyrrolidinone (20 mL) was added hexane-washed sodium hydride (26 mmol, 1.01 g). The reaction mixture was stirred at ambient temperature for 15 minutes, then heated to 65 degrees Celsius for 30 minutes. Bromo-

-252-

4-fluorobenzene (25 mmol, 4.38 g) was added, and the solution was heated at 120 degrees Celsius for 24 hours. The reaction mixture was permitted to cool to ambient temperature, was diluted with water (100 mL),  
5 and was extracted with ethyl acetate (150 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and concentrated in vacuo to afford an oil, which was further purified by passage through silica pad, eluting with ethyl acetate. 7.28  
10 g (82%) were obtained. MS calculated for  $C_{16}H_{22}NO_3Br$ : 356, found 356.

Part B: To a solution of the bromide of part A (20 mmol, 7.2 g) in dioxane (20 mL) was added 4N HCl (50 mL). The solution was stirred at ambient  
15 temperature for two hours, then concentrated to give a solid. The solid was triturated with diethyl ether, affording the desired piperidine hydrochloride (5.8 g 99%).

Part C: To a solution of 3,4-  
20 dimethoxybenzenesulfonyl chloride (18 mmol, 4.26 g) in acetonitrile (75 mL) was added the hydrochloride from part B (20 mmol, 5.8 g), followed by triethylamine (36 mmol, 7.5 mL) and N,N-dimethylaminopyridine (100 mg). The solution was  
25 stirred at ambient temperature for 75 hours. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (300 mL). The ethyl acetate layer was washed with brine (100 mL), and dried over magnesium sulfate. Concentration followed by  
30 chromatography (1:1 hexane:ethyl acetate) provided the desired sulfonamide as a solid (5.45 g, 66%). MS calculated for  $C_{19}H_{22}BrNSO_5$ , 456, found 456.

-253-

Part D: To a solution of the compound of Part C (2.96 g, 6.49 mmol) in ethylene glycol dimethyl ether (30 mL) at ambient temperature under an atmosphere of nitrogen was added

5 tetrakis(triphenylphosphine)palladium(0) (0.375 g, 0.325 mmol). After stirring for 5 minutes, 2-methoxyphenylboronic acid (1.18 g, 7.79 mmol) was added followed by a solution of sodium carbonate (0.954 g, 9.00 mmol) in water (18 mL). The mixture

10 was refluxed for 1.5 hours and then stirred overnight (about 18 hours) at ambient temperature. The mixture was diluted with water (50 mL) and extracted with methylene chloride (50 mL). The solution was filtered through a silica bed and concentrated in

15 vacuo to a black solid. Chromatography (on silica, acetone/hexane) provided the biphenyl as a white solid (2.69 g, 86% yield); Anal. calcd for  $C_{26}H_{29}NO_6S$ : C, 64.58; H, 6.04; N, 2.90; S, 6.63. Found: C, 64.30; H, 6.16; N, 2.86; S, 6.90. MS (EI)  $MH^+$  calcd.

20 for  $C_{26}H_{29}NO_6S$  484, found 484.

Part E: To a solution of the biphenyl of Part D (2.85 g, 5.89 mmol) in THF (80 mL) at -80 degrees Celsius under a nitrogen atmosphere was added a solution of 1.6 M n-butyllithium in hexane (5.17

25 mL, 8.27 mmol). After stirring at ambient temperature for 30 minutes, the solution was cooled to -80 degrees Celsius and carbon dioxide was bubbled into the solution for 7 minutes. The solution was diluted with 1N HCl (50 mL) and extracted with ethyl

30 acetate (3x50 mL). The organic layer was washed with water (2x50 mL) and brine (50 mL), dried with  $MgSO_4$ , and concentrated in vacuo to provide the carboxylic acid as a tan solid (3.00 g, 96% yield) ); Anal.

-254-

calcd for  $C_{27}H_{29}NO_8S$ : C, 61.47; H, 5.54; N, 2.65; S, 6.08. Found: C, 61.46; H, 5.94; N, 2.48; S, 5.70. MS (EI)  $MH^+$  calcd. for  $C_{27}H_{29}NO_8S$  528, found 528.

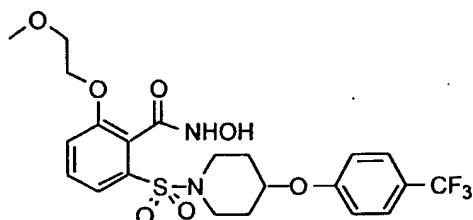
Part F: To a solution of the carboxylic acid of Part E (2.92 g, 5.53 mmol) and DMF (2 drops, catalytic amount) in 1,2-dichloroethane (50 mL) was added oxalyl chloride (4.07 mL, 46.7 mmol). After stirring for 1.5 hours at ambient temperature under a nitrogen atmosphere, the solution was concentrated in vacuo to a yellow oil. To the oil were added N-methylmorpholine (1.57 mL, 14.2 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.66 g, 14.2 mmol), and 1,2-dichloroethane (19 mL). After stirring for about 20 hours at ambient temperature under an atmosphere of nitrogen, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (3x50 mL). The organic layer was washed with 1N HCl (50 mL), saturated  $NaHCO_3$  (50 mL), water (50 mL), and brine (50 mL), dried with  $MgSO_4$ , and concentrated in vacuo to a tan solid. Chromatography (on silica, ethyl acetate/hexane) provided the O-protected hydroxamate as a white solid (2.41 g, 69% yield); MS (EI)  $MH^+$  calcd. for  $C_{32}H_{38}N_2O_9S$  627, found 627.

Part G: To a solution of acetyl chloride (2.61 mL, 38.1 mmol) in MeOH (39 mL) was added the O-protected hydroxamate of Part F (2.39 g, 3.81 mmol) and stirred at ambient temperature under a nitrogen atmosphere for 1.5 hours. The solution was concentrated, triturated with ether, concentrated, and dried to give a white solid. Chromatography (on silica, MeOH/ $CHCl_3$ ) provided the title compound as a white solid (1.36 g, 66% yield); Anal. calcd for  $C_{27}H_{30}N_2O_8S$ : C, 59.77; H, 5.57; N, 5.16; S, 5.91.

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Found: C, 57.60; H, 5.17; N, 5.04; S, 5.67. MS (EI)  
MH<sup>+</sup> calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>8</sub>S 543

5 Example 23: Preparation of N-Hydroxy-2-(2-methoxy-  
ethoxy)-6-[[4-[4-(trifluoromethyl)-  
phenoxy]-1-piperidinyl]sulfonyl]benzamide



Part A: A solution of 1-[(3-fluorophenyl)-  
10 sulfonyl]-4-[4 (trifluoromethyl)phenoxy]piperidine  
(7.00 g, 17.4 mmol), 60% sodium hydride (1.13 g, 28.2  
mmol) and 2-methoxy-1-ethanol (2.19 mL, 27.7 mmol) in  
1-methyl-2-pyrrolidinone (10 mL) was heated at 120  
degrees Celsius for 5 hours. The solution was  
15 diluted with water (300 mL) and extracted with ethyl  
acetate (3x100 mL). The organic layer was washed  
with water (2x100 mL) and brine (100 mL), dried with  
MgSO<sub>4</sub>, and concentrated in vacuo to a brown paste.  
Recrystallization from methyl tert-butyl ether/hexane  
20 provided the ether as a white solid (6.59 g, 83%  
yield). The proton NMR spectrum was consistent for  
the desired ether.

Part B: To a solution of the ether of Part  
A (6.59 g, 14.3 mmol) in THF (120 mL) at -10 degrees  
25 Celsius under a nitrogen atmosphere was added a  
solution of 1.7 M t-butyllithium in pentane (16.8 mL,  
26.8 mmol). After stirring at -60 degrees Celsius  
for 30 minutes, carbon dioxide was bubbled into the  
solution for 7 minutes, the resulting solution was

-256-

poured into a solution of 1N HCl (100 mL) and water (500 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with 1N HCl (100 mL), water (2x100 mL) and brine (100 mL), dried with 5 MgSO<sub>4</sub>, and concentrated *in vacuo*. Chromatography (acetic acid/ MeOH/CHCl<sub>3</sub>) provided the carboxylic acid as a yellow oil (4.67 g, 64% yield) ); Anal. calcd for C<sub>22</sub>H<sub>24</sub>NO<sub>7</sub>F<sub>3</sub>S: C, 52.48; H, 4.80; N, 2.78; S, 6.37. Found: C, 52.49; H, 4.70; N, 2.69; S, 6.31. MS (EI) 10 MH<sup>+</sup> calcd. for C<sub>22</sub>H<sub>24</sub>NO<sub>7</sub>F<sub>3</sub>S 504, found 504.

Part C: To a solution of the carboxylic acid of Part B (5.45 g, 10.8 mmol) and DMF (4 drops, catalytic amount) in dichloromethane (99 mL) was added oxalyl chloride (8.03 mL, 92.0 mmol). After 15 stirring for 2 hours at ambient temperature, the solution was concentrated *in vacuo* to a dark brown mixture. To the mixture were added N-methylmorpholine (4.76 mL, 43.3 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (5.07 g, 43.3 mmol), and 20 dichloromethane (77 mL). After stirring for about 4 hours at ambient temperature, the solution was washed with water, 1.0 N HCl, saturated NaHCO<sub>3</sub>, water, and brine, dried with MgSO<sub>4</sub>, and concentrated *in vacuo* to a paste. Chromatography (on silica, MeOH/ethyl 25 acetate) provided the O-protected hydroxamate as a pink solid (5.23 g, 80% yield); Anal. calcd for C<sub>27</sub>H<sub>33</sub>N<sub>2</sub>O<sub>8</sub>F<sub>3</sub>S: C, 53.81; H, 5.52; N, 4.65; S, 5.32. Found: C, 53.67; H, 5.43; N, 4.77; S, 5.17. MS (EI) MH<sup>+</sup> calcd. C<sub>27</sub>H<sub>33</sub>N<sub>2</sub>O<sub>8</sub>F<sub>3</sub>S for 603, found 603.

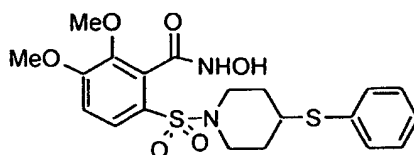
30 Part D: A solution of acetyl chloride (5.90 mL, 86.3 mmol) in MeOH (89 mL) was added to the O-protected hydroxamate of Part C (5.20 g, 8.63 mmol) and stirred at ambient temperature for 3 hours. The

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solution was concentrated, triturated with ether, and concentrated to give an off white solid.

Chromatography (on silica, MeOH/methylene chloride) provided the title compound as a white solid (2.25 g, 50% yield); Anal. calcd for  $C_{22}H_{25}N_2O_7S$ : C, 50.96; H, 4.86; N, 5.40; S, 6.18. Found: C, 50.57; H, 4.91; N, 5.37; S, 6.08. MS (EI)  $MH^+$  calcd. for  $C_{22}H_{25}N_2O_7S$  519, found 519.

- 10 Example 24: Preparation of N-Hydroxy-2,3-dimethoxy-6-[[4-(phenylthio)-1-piperidinyl]-sulfonyl]benzamide



- Part A: 4-Hydroxypiperidine (55 mmol, 5.56 g) was diluted with acetonitrile (100 mL), triethylamine (55 mmol, 7.7 mL), and N,N-dimethylaminopyridine (500 mg). 3,4-dimethoxy-benzenesulfonyl chloride (50 mmol, 11.84 g) was added. The mixture was stirred overnight (about 18 hours), then concentrated by rotary evaporation. The residue was diluted with water (100 mL) and extracted with dichloromethane (2 X 150 mL). The combined organic phases were dried using magnesium sulfate, filtered through a silica plug, and concentrated to afford the desired alcohol as a foam (7.31 g, 51%).

- Part B: The alcohol from Part A (6.39 g, 22.4 mmol) was combined with methylene chloride (65 mL) and triethylamine (3.46 mL, 25 mmol). The solution was chilled to zero degrees Celsius. Methanesulfonyl chloride (1.79 mL, 23 mmol) was added. The reaction was stirred at ambient

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temperature for 4 hours, then diluted to 150 ml with additional methylene chloride, and washed with water (2 X 25 mL). The organic phase was dried over magnesium sulfate, filtered through silica, and concentrated to provide the mesylate as a white solid (3.51 g, 41%).

Part C: 60% Sodium hydride in mineral oil (324 mg, 8.1 mmol) was washed with hexanes. The washed hydride was covered with N,N-dimethylformamide (12 mL) and chilled to zero degrees Celsius. Thiophenol (0.83 mL, 8.1 mmol) was added, and the mixture was stirred for 20 minutes. Solid mesylate from Part B, above, (3.0 g, 7.9 mmol) was added. Mesylate displacement was slow at ambient temperature; the reaction was warmed at 55 degrees Celsius for 3 hours. Work-up comprised of azeotropic removal of the DMF assisted by toluene, followed by chromatography of the residue, affording 1.45 g (44%) of the sulfide as a white foam.

Part D: The sulfide was dissolved in tetrahydrofuran (24 mL) and cooled to zero degrees Celsius. T-BuLi (1.7 M in pentane, 4.1 mL) was added over 1 minute. After 15 minutes, the reaction was quenched with carbon dioxide gas. After 10 minutes, the mixture was acidified using concentrated HCl, concentrated, and chromatographed to give the desired acid as a foam (1.067 g, 70%).

Part E: The acid from Part C was diluted with methylene chloride (15 mL). Three drops of N,N-dimethylformamide were added, followed by oxalyl chloride (0.35, 4 mmol). The reaction was stirred at ambient temperature for 2 hours, then concentrated. The crude acid chloride was added using about 3 mL of



-259-

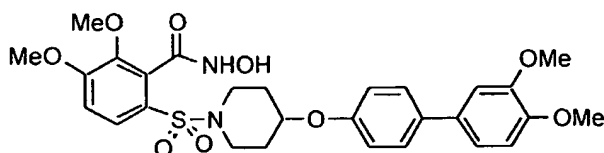
methylene chloride to a mixture of tetrahydropyran-hydroxylamine (0.47 g, 4 mmol), pyridine (0.47 ml, 6 mmol) and acetonitrile (3 mL). The mixture was stirred overnight (about 18 hours), then subjected to aqueous extraction (50 mL methylene chloride/50 mL water). The organic phase was dried over magnesium sulfate, concentrated, and chromatographed to afford the O-THP hydroxamate as a foam (619 mg).

The O-THP hydroxamate (614 mg) was diluted with dry methanol (20 mL). Acetyl chloride (0.6 mL, 8 mmol) was added. After 1 hour, the mixture was concentrated and chromatographed, affording the desired hydroxamate as a foam (428 mg, 31%). MS (EI) MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: 453, found 453.

15

The following analogs were made in good yield using similar procedures:

Example 25: 6-[[4-[(3'-Dimethoxy[1,1'-biphenyl]-4-yl)-1-piperidinyl]sulfonyl]-N hydroxy-2,3-dimethoxybenzamide

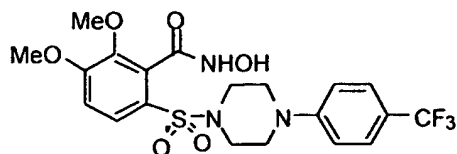


MS (EI) MH<sup>+</sup> calculated for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>9</sub>S: 573, found 573.

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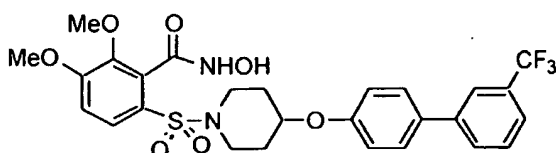
Example 26: N-Hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenyl]-1-piperazinyl]sulfonyl]benzamide

- 260 -



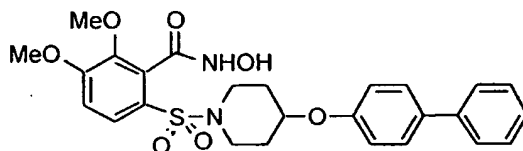
MS (EI) calculated for  $C_{20}H_{22}F_3N_3O_6S$ : 490, found 490.

Example 27: N-Hydroxyl-2,3-dimethoxy-6-[[4-[[3'-(trifluoromethyl)[1,1'-biphenyl]-4-ylloxy]-1-piperidinyl]sulfonyl]benzamide



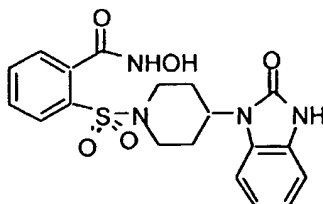
MS (EI) calculated for  $C_{27}H_{27}F_3N_2O_7S$ : 581, found 581.

Example 28: 6-[[4-(1,1'-Biphenyl)-4-yloxy)-1-piperidinyl]sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide



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Example 29: 2-[[4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]sulfonyl]-N-hydroxybenzamide

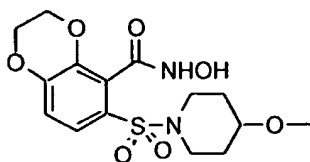


MS (EI) calculated for  $C_{19}H_{20}N_4O_5S$ : 417, found 417.

Example 30: 2,3-Dihydro-N-hydroxy-6-[(4-methoxy-

-261-

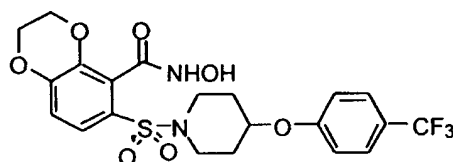
1-piperidinyl)sulfonyl]-1,4-benzodioxin-  
5-carboxamide



MS (EI) calculated for  $C_{15}H_{20}N_2O_7S$ : 372, found 373.

5

Example 31: 2,3-Dihydro-N-hydroxy-6-[[4-  
 [4-(trifluoromethyl)phenoxy]-1-  
 piperidinyl)sulfonyl]-1,4-  
benzodioxin-5-carboxamide

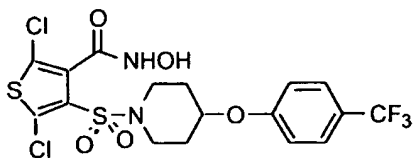


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MS (EI) calculated for  $C_{21}H_{21}F_3N_2O_7S$ : 502, found 503.

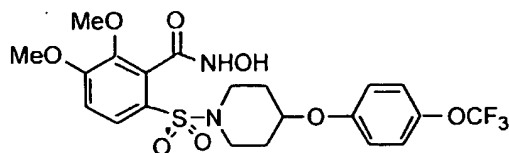
Example 32: 2,5-Dichloro-N-hydroxy-4-[[4-  
 {4-(trifluoromethyl)phenoxy}-1-  
 piperidinyl)sulfonyl]-3-  
thiophenecarboxamide

15



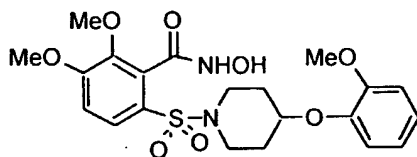
Example 33: N-Hydroxy-2,3-dimethoxy-6-[[4-  
 [4-(trifluoromethoxy)phenoxy]-  
 1-piperinyl]sulfonyl]benzamide

20



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Example 34: N-Hydroxy-2,3-dimethoxy-6-[[4-(2-methoxyphenoxy)-1-piperidinyl]-sulfonyl]benzamide

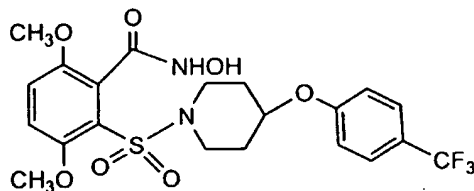


5

Anal. Calc.'d for  $C_{21}H_{16}N_2O_8S$ : C, 50.07; H, 5.62; N, 6.00. Found: C, 53.77; H, 5.64; N, 5.79.

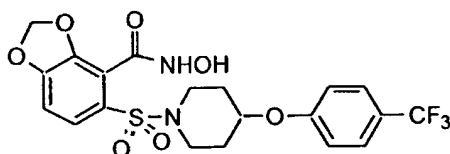
Example 35: N-Hydroxy-3,6-dimethoxy-2-[[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide

10



Example 36: N-Hydroxyl-5-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl-1,3-benzodioxole-4-carboxamide

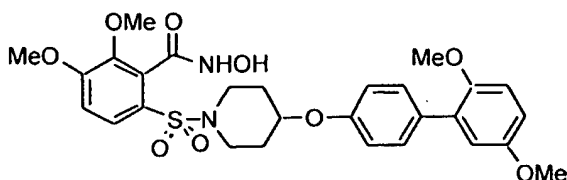
15



MS (EI) calculated for  $C_{20}H_{19}F_3N_2O_7S$ : 489, found 489.

Example 37: 6-[[4-[(2',5'-Dimethoxy[1,1'-biphenyl]-4-yl)oxy]-1-piperidinyl]sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide

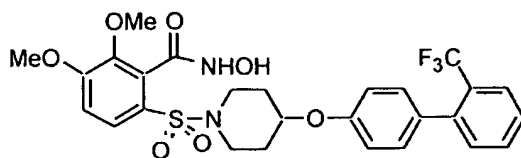
20



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Anal. Calc.'d for  $C_{28}H_{32}N_2O_9S$ : C, 58.73; H, 5.63; N, 4.89. Found: C, 58.55; H, 5.82; N, 4.81.

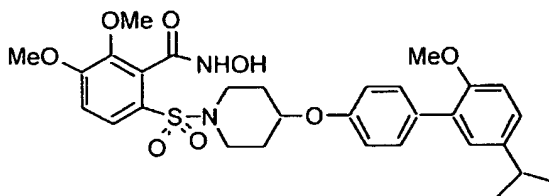
5 Example 38: N-Hydroxy-2,3-dimethoxy-6-[[4-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-ylloxy]-1-piperidinyl]sulfonyl]benzamide



Anal. Calc.'d for  $C_{27}H_{27}F_3N_2O_7S$ : C, 55.86; H, 4.69; N, 4.83. Found: C, 55.77; H, 4.75; N, 4.77.

10

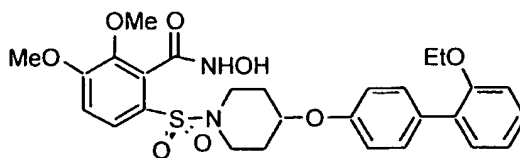
Example 39: N-Hydroxy-2,3-dimethoxy-6-[[4-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-ylloxy]-1-piperidinyl]sulfonyl]benzamide



15 Anal. Calc.'d for  $C_{30}H_{36}N_2O_8S$ : C, 61.63; H, 6.21; N, 4.79. Found: C, 61.36; H, 6.29; N, 4.64.

Example 40: 6-[[4-[(2'-Ethoxy[1,1'-biphenyl]-4-yl)oxy]-1-piperidinyl]sulfonyl]-N-hydroxyl-2,3-dimethoxybenzamide

20

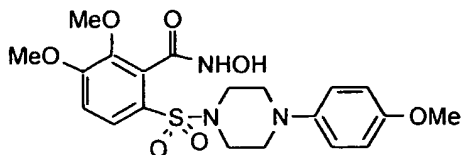


Anal. Calc.'d for  $C_{28}H_{32}N_2O_8S$ : C, 60.42; H, 5.79; N, 5.03. Found: C, 60.30; H, 5.94; N, 4.88.

25 Example 41: N-Hydroxy-2,3-dimethoxy-6-[[4-(4-

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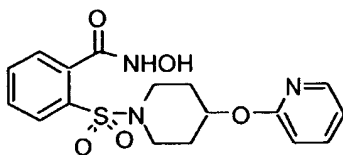
methoxyphenyl)-1-piperazinyl]sulfonyl]-  
benzamide, monohydrochloride



MS (EI) MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>7</sub>S (free base):

5 452, found 452.

Example 42: N-hydroxyl-2-[[4-(2-pyridinyloxy)-1-piperidinyl]sulfonyl]benzamide,  
monohydrochloride



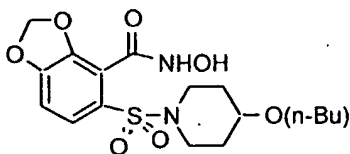
10

MS (EI) MH<sup>+</sup> calculated for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>7</sub>S (free base):

378, found 378.

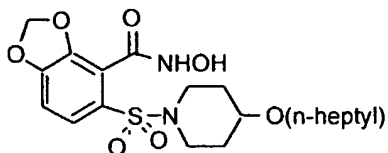
Example 43: 5-[(4-Butoxy-1-piperidinyl)sulfonyl]-  
N-hydroxy-1,3-benzodioxole-4-carboxamide

15



Anal. Calc.'d for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>S: C, 50.99; H, 6.04; N, 7.00. Found: C, 50.97; H, 6.27; N, 6.88.

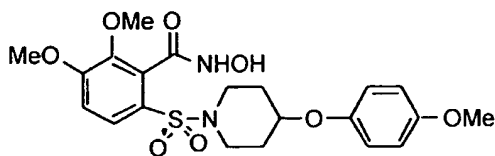
20 Example 44: 5-[(4-Heptyloxy-1-piperidinyl)sulfonyl]-  
N-hydroxy-1,3-benzodioxole-4-carboxamide



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Anal. Calc.'d for  $C_{20}H_{30}N_2O_7S$ : C, 54.28; H, 6.33; N, 6.33. Found: C, 53.91; H, 7.10; N, 6.25.

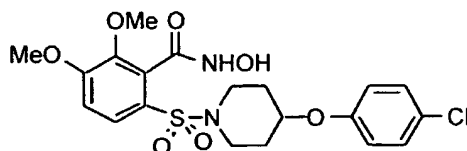
5 Example 45: N-Hydroxy-2,3-dimethoxy-6-[[4-(4-methoxyphenoxy)-1-piperidinyl]-sulfonyl]benzamide



Anal. Calc.'d for  $C_{21}H_{26}N_2O_8S$ : C, 54.07; H, 5.62; N, 6.00. Found: C, 53.69; H, 5.87; N, 5.79.

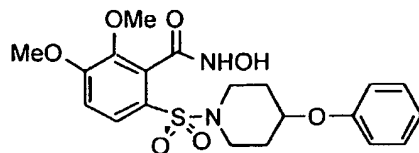
10

Example 46: 6-[[4-(4-Chlorophenoxy)-1-piperidinyl]-sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide



15 Anal. Calc.'d for  $C_{20}H_{23}ClN_2O_8S$ : C, 51.01; H, 4.92; N, 5.95. Found: C, 50.62; H, 4.93; N, 5.92.

Example 47: N-Hydroxy-2,3-dimethoxy-6-[(4-phenoxy)-1-piperidinyl]sulfonyl]benzamide

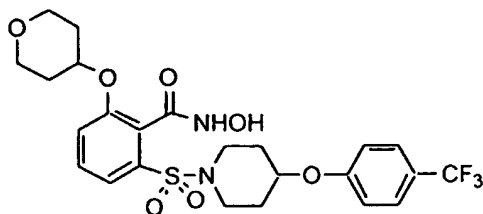


20

MS (EI) calculated for  $C_{20}H_{24}N_2O_7S$ : 436, found 437.

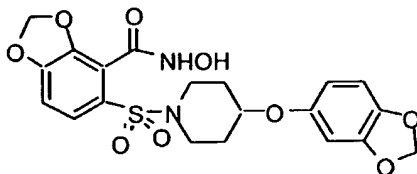
25 Example 48: N-Hydroxy-2-[(tetrahydro-2H-pyran-4-yl)oxy]-6-[[4-(trifluormethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide

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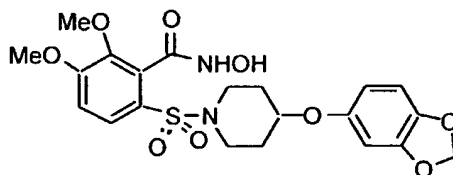


Anal. Calc.'d for  $C_{24}H_{27}F_3N_2O_7S$ : C, 52.94; H, 5.00; N, 5.14. Found: C, 52.64; H, 4.92; N, 5.02.

- 5 Example 49: 5-[[4-((1,3-Benzodioxol)-5-yloxy)-1-piperidinyl]sulfonyl]-N-hydroxy-1,3-benzodioxole-4-carboxamide

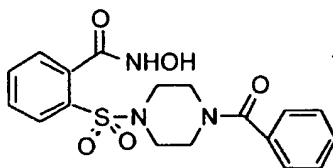


- 10 Example 50: 6-[[4-(1,3-Benzodioxole-5-yloxy)-1-piperidinyl]sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide



MS (EI) calculated for  $C_{21}H_{24}N_2O_9S$ : 481, found 481.

- 15 Example 51: 2-[(4-Benzoyl-1-piperazinyl)sulfonyl]-N-hydroxybenzamide

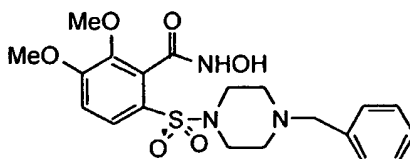


MS (EI)  $MH^+$  calculated for  $C_{18}H_{19}N_3O_5S$ : 390, found 390.

- 20 Example 52: N-Hydroxy-2,3-dimethoxy-6-[[4-(phenylmethyl)-1-piperazinyl]sulfonyl]-



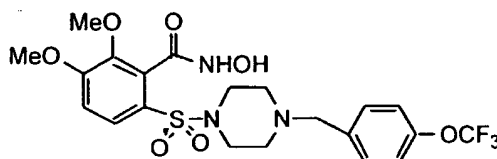
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benzamide, monohydrochloride

MS (EI) MH<sup>+</sup> calculated for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>S (free base) :  
436, found 436.

5

Example 53: N-Hydroxy-2,3-dimethoxy-6-[[4-[[4-(trifluoromethoxy)phenyl]methyl]-1-piperazinyl]sulfonyl]benzamide,  
monohydrochloride

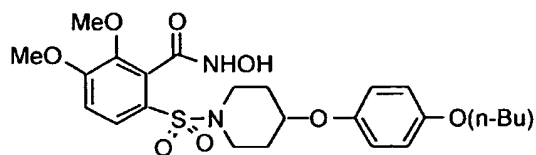


10

MS (EI) MH<sup>+</sup> calculated for C<sub>21</sub>H<sub>24</sub>F<sub>3</sub>N<sub>3</sub>O<sub>7</sub>S: 520, found  
520.

Example 54: 6-[[4-(4-Butoxyphenoxy)-1-piperidinyl]-  
sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide

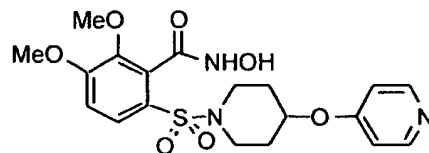
15



MS (EI) MH<sup>+</sup> calculated for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>8</sub>S: 509, found 509.

Example 55: N-Hydroxy-2-[[4-(4-pyridinyloxy)-1-piperidinyl]sulfonyl]benzamide,  
monohydrochloride

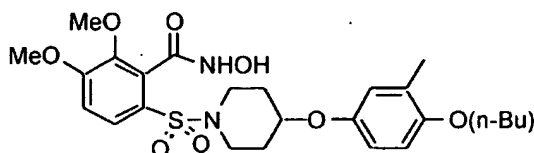
20



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MS (EI) MH<sup>+</sup> calculated for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S (free base):  
378, found 378.

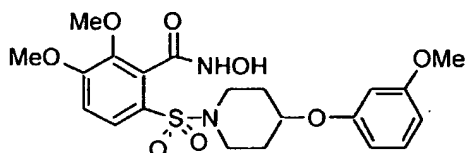
Example 56: 6-[[4-(4-Butoxy-3-methylphenyl)-1-piperazinyl]sulfonyl]-N-hydroxy-2,3-dimethoxybenzamide, monohydrochloride



MS (EI) MH<sup>+</sup> calculated for C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>7</sub>S (free base):  
508, found 508.

10

Example 57: N-Hydroxy-2,3-dimethoxy-6-[[4-(3-methoxyphenoxy)-1-piperidinyl]sulfonyl]benzamide



Anal. Calc.'d for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>S: C, 54.07; H, 5.62; N, 6.00. Found: C, 53.77; H, 5.64; N, 5.79.

Example 58: In Vitro Metalloprotease Inhibition

The compounds prepared in the manner described in the Examples above were assayed for activity by an *in vitro* assay. Following the procedures of Knight et al., *FEBS Lett.* 296(3):263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin-activated MMPs were incubated with various concentrations of the inhibitor compound at room temperature for 5 minutes.

More specifically, recombinant human MMP-13, MMP-1 and MMP-2 enzymes were prepared in

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laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a baculovirus as discussed in V.A. Luckow, Insect Cell Expression Technology, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, 67:4566-4579 (1993); O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al., The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992) for further details on use of baculovirus expression systems. The expressed enzyme was purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay.

MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr. Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Further specifics for preparation and use of these enzymes can be found in the scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, Ca (1992) and the citations

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therein, and Frije et al., J. Biol. Chem., 26(24):  
16766-16773 (1994).

The enzyme substrate is a methoxycoumarin-  
containing polypeptide having the following sequence:

5           MCA-ProLeuGlyLeuDpaAlaArgNH<sub>2</sub>, wherein MCA  
is methoxycoumarin and Dpa is 3-(2,4-dinitrophenyl)-  
L-2,3-diaminopropionyl alanine. This substrate is  
commercially available from Baychem as product  
M-1895.

10           The buffer used for assays contained 100 mM  
Tris-HCl, 100 mM NaCl, 10 mM CaCl<sub>2</sub> and 0.05 percent  
polyethyleneglycol (23) lauryl ether at a pH value of  
7.5. Assays were carried out at room temperature,  
and dimethyl sulfoxide (DMSO) at a final  
15           concentration of 1 percent was used to dissolve  
inhibitor compound.

          The assayed inhibitor compound in  
DMSO/buffer solution was compared to an equal amount  
of DMSO/buffer with no inhibitor as control using  
20           Microfluor™ White Plates (Dynatech). The inhibitor  
or control solution was maintained in the plate for  
10 minutes and the substrate was added to provide a  
final concentration of 4 μM.

          In the absence of inhibitor activity, a  
25           fluorogenic peptide was cleaved at the gly-leu  
peptide bond, separating the highly fluorogenic  
peptide from a 2,4-dinitrophenyl quencher, resulting  
in an increase of fluorescence intensity (excitation  
at 328 nm/emission at 415 nm). Inhibition was  
30           measured as a reduction in fluorescent intensity as a  
function of inhibitor concentration, using a Perkin  
Elmer L550 plate reader. The IC<sub>50</sub> values were  
calculated from those values. The results are set

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forth in the Inhibition Tables A and B below,  
reported in terms of  $IC_{50}$  to three significant  
figures, where appropriate.

Inhibition Table A

( $IC_{50}$  values in nM)

5

Example	MMP-1	MMP-2	MMP-13
1	>10,000	10	45
2	900	0.3	2
3	>10,000	148	1000
4	>10,000	>10,000	>10,000
5	>10,000	3500	>10,000
6	>10,000	--	4000
7	>10,000	--	>10,000
8	>10,000	--	>10,000
9	>10,000	45.0	1500
10	>10,000	70.0	520
11	>10,000	2,300	2,200
12	>10,000	2.2	33.0
13D	>10,000	3300	3800
13	>10,000	1.3	28.5
14	>10,000	35	900
15	>10,000	3,500	9,000
16	>10,000	2.4	2.7
17	>10,000	1,800	2,000
18	--	--	--
19	>10,000	5.0	12.3
20	>10,000	1.8	14.8
21	>10,000	5.9	63

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Inhibition Table B  
(IC<sub>50</sub> values in nM)

Example Number	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13	MT1- MMP
22	>10,000	15.5	170	800	300	5.5	2500
23	>10,000	1.0				4.3	
24	>10,000	0.9	400	10.7	10.0	3.0	25.4
25	>10,000	3.3	100	115	370	2.6	1700
26	>10,000	6.5	1750	37.2	970	40	1920
27	>10,000	3.3	300	210	520	3.0	690
28	>10,000	0.4				1.8	
29	>10,000	370				2000	
30	>10,000	>10,000				>10,000	
31	>10,000	1.4				7.7	
32	>10,000	110				730	
33	>10,000	0.9	100		1.5	5.0	360
34	>10,000	330				2500	
35	>10,000	21				110	
36	>10,000	3.0	600	12.2	8.0	18.0	300
37	---	---				---	
38		20		1700		82	
39		120		400		100	
40		80		4400		50	
41	>10,000	6.0	8000	120	470	100	4000
442	>10,000	42				1200	
43	>10,000	200				3700	
44	>10,000	206				330	
45	>10,000	1.8	900	11.4	3.0	13.9	300
46	>10,000	0.3				1.5	
47	>10,000	1.1				6.7	
48	>10,000	1.0				2.2	
49	>10,000	1.1				19	
50	>10,000	1.1	1300	12.2	9.0	18.6	270
51	>10,000	1000				6700	
52		1500		>10,000		4000	
53	>10,000	240				1900	
54	>10,000	0.8	31.6	70.0	2.0	1.6	200
55	>10,000	5.9				63	
56	>10,000	9.0				20.0	
57	>10,000	12.1				250	

5

Example 59: In Vivo Angiogenesis Assay

The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. See, A Model

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of Angiogenesis in the Mouse Cornea; Kenyon, BM, et al., Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8.

In this assay, uniformly sized Hydron™ pellets containing bFGF and sucralfate are prepared and surgically implanted into the stroma mouse cornea adjacent to the temporal limbus. The pellets are formed by making a suspension of 20 µL sterile saline containing 10 µg recombinant bFGF, 10 mg of sucralfate and 10 µL of 12 percent Hydron™ in ethanol. The slurry is then deposited on a 10 x 10 mm piece of sterile nylon mesh. After drying, the nylon fibers of the mesh are separated to release the pellets.

The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet is placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet is then advanced to the temporal end of the pocket. Antibiotic ointment is then applied to the eye.

Mice are dosed on a daily basis for the duration of the assay. Dosing of the animals is based on bioavailability and overall potency of the compound. an exemplary dose is 50 mg/kg bid, po. Neovascularization of the corneal stroma begins at

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about day three and is permitted to continue under the influence of the assayed compound until day five. At day five, the degree of angiogenic inhibition is scored by viewing the neovascular progression with a slit lamp microscope.

The mice are anesthetized and the studied eye is once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet is measured. In addition, the contiguous circumferential zone of neovascularization is measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis is calculated as follows.

$$area = \frac{(0.4 \times \text{clock hours} \times 3.14 \times \text{vessel length (in mm)})}{2}$$

15

The studied mice are thereafter compared to control mice and the difference in the area of neovascularization is recorded. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

It will be observed that numerous modifications and variations can be effectuated without departing from the spirit and scope of the novel concepts of the present invention. No limitation with respect to the specific examples presented is intended or should be inferred. The disclosure is intended to encompass such modifications as fall within the scope of the claims.

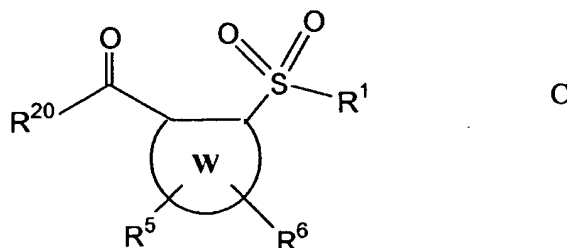


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## WHAT IS CLAIMED IS:

1. A compound corresponding to Formula C,  
or a pharmaceutically acceptable salt thereof:

5



wherein

the ring structure W is a 5- or 6-membered  
10 aromatic or heteroaromatic ring;

R<sup>1</sup> is (i) a substituent containing a 5- or  
6-membered cyclohydrocarbyl, heterocyclo, aryl or  
heteroaryl radical that is bonded directly to the  
depicted SO<sub>2</sub>-group and having a length greater than  
15 about that of a hexyl group and less than about that  
of an eicosyl group, said R<sup>1</sup> defining a three-  
dimensional volume, when rotated about an axis drawn  
through the SO<sub>2</sub>-bonded 1-position and the 4-position  
of a 6-membered ring radical or drawn through the  
20 SO<sub>2</sub>-bonded 1-position and the center of 3,4-bond of a  
5-membered ring radical, whose widest dimension in a  
direction transverse to the axis of rotation is about  
that of one furanyl ring to about that of two phenyl  
rings;

25 R<sup>5</sup> and R<sup>6</sup> are independently selected from  
the group consisting of a hydrido, alkyl, cycloalkyl,  
acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy,  
haloalkyl, haloalkyloxy, hydroxyalkyl, a

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R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

5                   or R<sup>5</sup> and R<sup>6</sup> together with the atoms to which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members; and

                  R<sup>20</sup> is (a) -O-R<sup>21</sup>, where R<sup>21</sup> is selected  
10   from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group and a pharmaceutically acceptable cation, (b) -NR<sup>13</sup>-O-R<sup>22</sup> wherein R<sup>22</sup> is a selectively removable protecting group and R<sup>13</sup> is a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl or benzyl group, (c) -NR<sup>13</sup>-O-  
15   R<sup>14</sup>, where R<sup>13</sup> is as before and R<sup>14</sup> is hydrido, a pharmaceutically acceptable cation or C(V)R<sup>15</sup> where V is O or S and R<sup>15</sup> is selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl,  
20   aryloxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, heteroaryl and amino C<sub>1</sub>-C<sub>6</sub>-alkyl group wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of  
25   an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, and C<sub>1</sub>-C<sub>6</sub>-alkanoyl radical, or (iii) wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered

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heterocyclo or heteroaryl ring, or (d)  $-NR^{23}R^{24}$ , where  $R^{23}$  and  $R^{24}$  are independently selected from the group consisting of a hydrido,  $C_1$ - $C_6$ -alkyl, amino  $C_1$ - $C_6$ -alkyl, hydroxy  $C_1$ - $C_6$ -alkyl, aryl, and an ar- $C_1$ - $C_6$ -alkyl group, or  $R^{23}$  and  $R^{24}$  together with the depicted nitrogen atom form a 5- to 8-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur;

wherein:

- 10  $R^b$  and  $R^c$  are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, 15 heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl, 20 heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, 25 heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl, thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxy carbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, aminosulfonyl wherein the amino nitrogen is (i) 30 unsubstituted or (ii) independently substituted with one or two  $R^d$  radicals, or the substituents on the amino group taken together with the amino nitrogen

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form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
5 two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
10 arylalkylcarbonyl, alkoxy carbonyl and an  
arylalkyloxycarbonyl group; and

$R^f$  is selected from the group consisting of  
a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,  
cyano, and a  $R^dR^e$  amino group.

15

2. The compound or salt according to claim  
1 wherein said  $R^1$  is (i) an  $-NR^7R^8$  group in which  $R^7$   
and  $R^8$  are independently selected from the group  
consisting of hydrido, hydrocarbyl, aryl, substituted  
20 aryl, arylhydrocarbyl, and substituted  
arylhydrocarbyl, or (ii)  $R^7$  and  $R^8$  are independently  
selected from the group consisting of a hydrido,  
alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl,  
 $R^a$ oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl,  
25 arylalkyl, heteroaryl, heteroarylalkyl, and a  
heterocyclo substituent, each of which substituent  
groups is optionally substituted with an -A-R-E-Y  
substituent;

in said -A-R-E-Y substituent, A is selected  
30 from the group consisting of

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- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- 5 (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- 10 (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- 15 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;
- 20 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,
- 25 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted
- 30 with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio,

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trifluoromethylalkyl, amino, alkoxycarbonylalkyl,  
alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,  
hydroxycarbonylalkylamino, nitro, hydroxy,  
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl  
5 group;

the group E is selected from the group  
consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- (2) -CON(R<sup>k</sup>) - or -(R<sup>k</sup>)NCO-;
- 10 (3) -CO-;
- (4) -SO<sub>2</sub>R<sup>G</sup>- or -R<sup>G</sup>SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly  
15 to Y; and

the moiety Y is absent or is selected from  
the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
20 heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
25 aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
30 perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
(ii) substituted with one or two groups independently

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selected from hydrido, alkyl, and an aralkyl group;

or

$R^7$  and  $R^8$  taken together with the nitrogen atom to which they are bonded form a group -G-A-R-E-Y

5 wherein

G is a N-heterocyclo group;

the substituent A is selected from the group consisting of

- (1) -O-;
- 10 (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- 15 (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- 20 (12) -CS-N(R<sup>k</sup>) - or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- 25 (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, 30 cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,

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heteroaryloxyalkyl, arylthioalkyl,  
heteroarylthioalkyl, cycloalkylthioalkyl, and a  
heterocycloalkylthioalkyl group wherein the aryl or  
heteroaryl or cycloalkyl or heterocycloalkyl  
5 substituent is (i) unsubstituted or (ii) substituted  
with one or two radicals selected from the group  
consisting of a halo, alkyl, perfluoroalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,  
10 alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,  
hydroxycarbonylalkylamino, nitro, hydroxy,  
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl  
group;

the moiety E is selected from the group  
15 consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>G</sup>- or -R<sup>G</sup>-SO<sub>2</sub>-;
- 20 (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly  
to Y; and

the moiety Y is absent or is selected from  
25 the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
30 trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,



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- aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, perfluoroalkyl, perfluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group;
- wherein  $R^a$  is selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl,  $R^bR^c$ aminoalkanoyl, haloalkanoyl,  $R^bR^c$ aminoalkyl, alkoxyalkyl, haloalkyl and an arylalkyloxy group;
- $R^g$  is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  $R^{hR^i}$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy,  $R^{hR^i}$ -aminocarbonyloxy,  $R^{hR^i}$ -aminocarbonyl,  $R^{hR^i}$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^{hR^i}$ -aminosulfonyl,  $R^{hR^i}$ -aminocarbonyl( $R^h$ )amino, trifluoromethyl-sulfonyl( $R^h$ )amino, heteroarylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )aminocarbonyl, alkylsulfonyl( $R^h$ )amino,

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arylcarbonyl(R<sup>h</sup>)aminosulfonyl, and an  
alkylsulfonyl(R<sup>h</sup>)aminocarbonyl substituent;

R<sup>h</sup> is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
5 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
10 hydroxyalkyl group, each of which groups is  
optionally substituted by one or two groups  
independently selected from R<sup>j</sup> substituents as are  
the substituents of the substituted aminoalkyl and  
substituted aminoalkanoyl groups;

15 R<sup>i</sup> is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
20 haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
hydroxyalkyl group, each of which groups are  
optionally substituted by one or two R<sup>j</sup> substituents;

R<sup>j</sup> is selected from the group consisting of  
25 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
30 unsubstituted aminoalkanoyl, halo alkanoyl and a  
hydroxyalkyl group, wherein the substituents of the  
substituted aminoalkyl and substituted aminoalkanoyl

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groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

5         $R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,  $R^{CR^d}$ amino carbonyl,  $R^{CR^d}$ aminosulfonyl,  $R^{CR^d}$ aminoalkanoyl and  $R^{CR^d}$ aminoalkysulfonyl.

10

3. The compound or salt according to claim 1 wherein said  $R^5$  and  $R^6$  are independently selected from the group consisting of a hydrido, hydrocarbyl, hydroxylhydrocarbyl, hydroxyl, amino, 15 dihydrocarbylamino, heterocyclo, heterocyclohydrocarbyl, heterocyclooxy, and a heterocyclothio group.

4. The compound or salt according to claim 20 1 wherein said 5- or 6-membered aromatic or heteroaromatic ring W is selected from the group consisting of a 1,2-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 4,5-pyridinylene, 2,3-pyrazinylene, 4,5-pyrimidinylene, and 5,6-pyrimidinylene group.

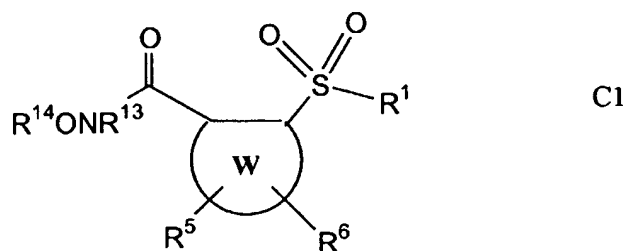
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5. The compound or salt according to claim 1 wherein said  $R^{20}$  is  $-NR^{13}-O-R^{14}$ .

6. The compound or salt according to claim 30 1 wherein said  $R^{20}$  is  $-NR^{13}-O-R^{22}$ .

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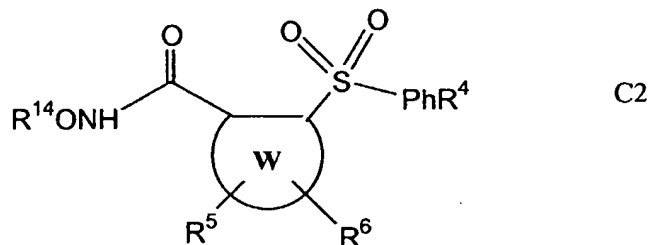
7. The compound or salt according to claim 1 wherein the compound corresponds in structure to Formula C1



5

wherein W, R<sup>1</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined before.

8. The compound or salt according to claim 1 wherein the compound corresponds in structure to Formula C2



Wherein W, R<sup>5</sup>, R<sup>6</sup> and R<sup>14</sup> are as defined before, Ph is phenyl substituted at its own 4-position with a substituent R<sup>4</sup>, wherein R<sup>4</sup> is a substituent that has a chain length of 3 to about 14 carbon atoms.

9. The compound or salt according to claim 8 wherein said R<sup>4</sup> substituent is selected from the group consisting of a phenyl group, a phenoxy group, a thiophenoxy group, an anilino group, a phenylazo

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group, a phenylureido, a benzamido, a nicotinamido,  
an isonicotinamido, a picolinamido group, a  
heterocyclo, heterocyclohydrocarbyl,  
arylheterocyclohydrocarbyl, arylhydrocarbyl,  
5 heteroarylhydrocarbyl, heteroarylheterocyclo-  
hydrocarbyl, arylhydrocarbyloxyhydrocarbyl,  
aryloxyhydrocarbyl, hydrocarboylhydrocarbyl,  
arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl,  
arylazoaryl, arylhydrazinoaryl, hydrocarbylthio-  
10 hydrocarbyl, hydrocarbylthioaryl, arylthio-  
hydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbyl-  
thioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl,  
arylhydrocarbylthioaryl, arylhydrocarbylamino,  
heteroarylhydrocarbylamino, and a heteroarylthio  
15 group.

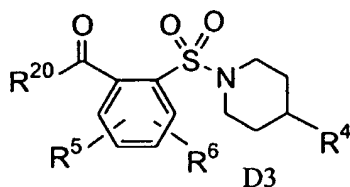
10. The compound or salt according to  
claim 9 wherein said R<sup>4</sup> substituent is itself  
substituted by one or more substituents selected from  
20 the group consisting of a halogen, hydrocarbyl,  
hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl,  
trifluoromethyl-hydrocarbyl, hydroxy, mercapto,  
hydroxycarbonyl, aryloxy, arylthio, arylamino,  
arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio,  
25 heteroarylamino, heteroarhydrocarbyl,  
hydrocarbyloxycarbonyl-hydrocarbyl, heterocyclooxy,  
hydroxycarbonyl-hydrocarbyl, heterocyclothio,  
heterocycloamino, cyclohydrocarbyloxy,  
cyclohydrocarbylthio, cyclohydrocarbylamino,  
30 heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio,  
heteroarylhydrocarbyl-amino, arylhydrocarbyloxy,  
arylhydrocarbylthio, arylhydrocarbylamino,  
heterocyclic, heteroaryl, hydroxycarbonyl-

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- hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarboyloxy, arylhydrocarboyloxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio,
- 5 hydrocarbyloxyhydrocarbylthio, hydrocarbyloxycarbonyl, hydroxycarbonyl-hydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-hydrocarbylthio, hydrocarbyloxycarbonylhydrocarbyloxy,
- 10 hydrocarbyloxycarbonylhydrocarbylthio, amino, hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino, heterocyclohydrocarbylcarbonylamino, arylhydrocarbylcarbonylamino, heteroarylcarbonylamino,
- 15 heteroarylhydrocarbylcarbonylamino, heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino, arylsulfonylamino, arylhydrocarbylsulfonylamino, heteroarylsulfonylamino, heteroarylhydrocarbylsulfonylamino, cyclohydrocarbylsulfonylamino,
- 20 heterocyclohydrocarbylsulfonylamino and N-monosubstituted or N,N-disubstituted aminohydrocarbyl group, wherein the substituent(s) on the nitrogen are selected from the group consisting of hydrocarbyl, aryl, arylhydrocarbyl, cyclohydrocarbyl,
- 25 arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl, and hydrocarboyl, or wherein the nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclic or heteroaryl ring group.

- 30 11. The compound or salt according to claim 1 wherein the compound corresponds in structure to Formula D3

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wherein  $R^5$ ,  $R^6$  and  $R^{20}$  are as defined  
 before, and  $R^4$  is a substituent that has a chain  
 5 length of 3 to about 14 carbon atoms.

12. The compound or salt according to  
 claim 11 wherein said  $R^4$  substituent is selected from  
 the group consisting of a phenyl group, a phenoxy  
 10 group, a thiophenoxy group, an anilino group, a  
 phenylazo group, a phenylureido, a benzamido, a  
 nicotinamido, an isonicotinamido, a picolinamido  
 group, a heterocyclo, heterocyclohydrocarbyl,  
 arylheterocyclohydrocarbyl, arylhydrocarbyl,  
 15 heteroarylhydrocarbyl, heteroarylheterocyclo-  
 hydrocarbyl, arylhydrocarbyloxyhydrocarbyl,  
 aryloxyhydrocarbyl, hydrocarboylhydrocarbyl,  
 arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl,  
 arylazoaryl, arylhydrazinoaryl, hydrocarbylthio-  
 20 hydrocarbyl, hydrocarbylthioaryl, arylthio-  
 hydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbyl-  
 thioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl,  
 arylhydrocarbylthioaryl, arylhydrocarbylamino,  
 heteroarylhydrocarbylamino, and a heteroarylthio  
 25 group.

13. The compound or salt according to  
 claim 12 wherein said  $R^4$  substituent is itself  
 substituted by one or more substituents selected from

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the group consisting of a halogen, hydrocarbyl, hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl, trifluoromethyl-hydrocarbyl, hydroxy, mercapto, hydroxycarbonyl, aryloxy, arylthio, arylamino, 5 arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio, heteroarylamino, heteroarhydrocarbyl, hydrocarbyloxycarbonyl-hydrocarbyl, heterocyclooxy, hydroxycarbonyl-hydrocarbyl, heterocyclothio, heterocycloamino, cyclohydrocarbyloxy, 10 cyclohydrocarbylthio, cyclohydrocarbylamino, heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio, heteroarylhydrocarbyl-amino, arylhydrocarbyloxy, arylhydrocarbylthio, arylhydrocarbylamino, heterocyclic, heteroaryl, hydroxycarbonyl- 15 hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarboyloxy, arylhydrocarboyloxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio, hydrocarbyloxyhydrocarbylthio, 20 hydrocarbyloxycarbonyl, hydroxycarbonyl-hydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-hydrocarbylthio, hydrocarbyloxycarbonylhydrocarbyloxy, hydrocarbyloxycarbonylhydrocarbylthio, amino, 25 hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino, heterocyclohydrocarbylcarbonylamino, arylhydrocarbylcarbonylamino, heteroarylcarbonylamino, heteroarylhydrocarbylcarbonylamino, 30 heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino, arylsulfonylamino, arylhydrocarbylsulfonylamino, heteroarylsulfonylamino, heteroarylhydrocarbylsulfonylamino, cyclohydrocarbylsulfonylamino,

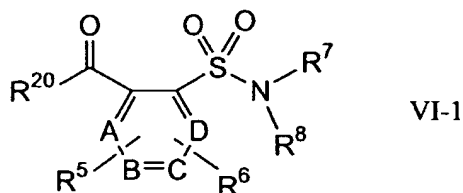


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heterocyclohydrocarbylsulfonylamino and N-monosubstituted or N,N-disubstituted aminohydrocarbyl group, wherein the substituent(s) on the nitrogen are selected from the group consisting of hydrocarbyl, aryl, arylhydrocarbyl, cyclohydrocarbyl, arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl, and hydrocarbonyl, or wherein the nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclic or heteroaryl ring group.

10

14. The compound or salt according to claim 1 wherein the compound corresponds in structure to Formula VI-1

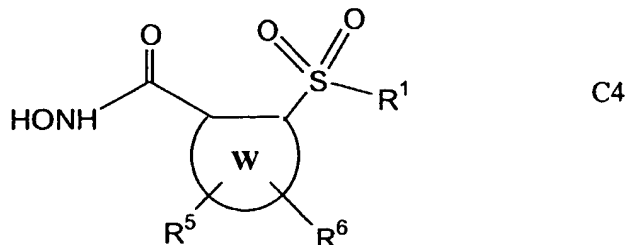


15

wherein each of  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^{20}$  is as defined before and each of A, B, C and D is carbon, nitrogen, sulfur or oxygen that is present or absent so that the depicted ring has 5- or 6-members.

20

15. A compound corresponding to Formula C4, or a pharmaceutically acceptable salt thereof:



25

wherein

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the ring structure W is a 5- or 6-membered aromatic or heteroaromatic ring;

R<sup>1</sup> is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO<sub>2</sub>-group and having a length greater than about that of a hexyl group and less than about that of an eicosyl group, said R<sup>1</sup> defining a three-dimensional volume, when rotated about an axis drawn through the SO<sub>2</sub>-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO<sub>2</sub>-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings; and

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

or R<sup>5</sup> and R<sup>6</sup> together with the atoms to which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members;

R<sup>b</sup> and R<sup>c</sup> are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl,

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perfluoroalkyl, trifluoromethylalkyl,  
perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl,  
heterocycloalkyl, heterocycloalkylcarbonyl, aryl,  
heterocyclo, heteroaryl, cycloalkylalkyl,  
5 aryloxyalkyl, heteroaryloxyalkyl,  
heteroarylalkoxyalkyl, heteroarylthioalkyl,  
arylsulfonyl, aralkanoyl, alkylsulfonyl,  
heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
10 alkyliminocarbonyl, aryliminocarbonyl,  
heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
15 alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
20 amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
25 two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
30 arylalkylcarbonyl, alkoxycarbonyl and an  
arylalkyloxycarbonyl group; and

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$R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen, aryl, alkoxy, cyano, and a  $R^{dRe}$  amino group.

5            16. The compound or salt according to claim 15 wherein said 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical of  $R^1$  is substituted with a substituent,  $R^4$ , that has a chain length of 3 to about 14 carbon  
10 atoms.

          17. The compound or salt according to claim 16 wherein said  $R^4$  substituent is selected from the group consisting of a phenyl group, a phenoxy group,  
15 a thiophenoxy group, an anilino group, a phenylazo group, a phenylureido, a benzamido, a nicotinamido, an isonicotinamido, a picolinamido group, a heterocyclo, heterocyclohydrocarbyl, arylheterocyclohydrocarbyl, arylhydrocarbyl,  
20 heteroarylhydrocarbyl, heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl, hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl, arylazoaryl, arylhydrazinoaryl, hydrocarbylthiohydrocarbyl,  
25 hydrocarbylthioaryl, arylthiohydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbylthioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl, arylhydrocarbylthioaryl, arylhydrocarbylamino, heteroarylhydrocarbylamino, and a heteroarylthio  
30 group.

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18. The compound or salt according to claim 17 wherein said R<sup>4</sup> substituent is itself substituted by one or more substituents selected from the group consisting of a halogen, hydrocarbyl, hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl, trifluoromethylhydrocarbyl, hydroxy, mercapto, hydroxycarbonyl, aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio, heteroarylamino, heteroarhydrocarbyl, hydrocarbyloxycarbonylhydrocarbyl, heterocyclooxy, hydroxycarbonylhydrocarbyl, heterocyclothio, heterocycloamino, cyclohydrocarbyloxy, cyclohydrocarbylthio, cyclohydrocarbylamino, heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio, heteroarylhydrocarbylamino, arylhydrocarbyloxy, arylhydrocarbylthio, arylhydrocarbylamino, heterocyclic, heteroaryl, hydroxycarbonylhydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarboyloxy, arylhydrocarboyloxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio, hydrocarbyloxyhydrocarbylthio, hydrocarbyloxycarbonyl, hydroxycarbonylhydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl, hydrocarbylhydroxycarbonylhydrocarbylthio, hydrocarbyloxycarbonylhydrocarbyloxy, hydrocarbyloxycarbonylhydrocarbylthio, amino, hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino, heterocyclohydrocarbylcarbonylamino, arylhydrocarbylcarbonylamino, heteroarylcarbonylamino, heteroarylhydrocarbylcarbonylamino, heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,

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arylsulfonylamino, arylhydrocarbylsulfonylamino, heteroarylsulfonylamino, heteroarylhydrocarbylsulfonylamino, cyclohydrocarbylsulfonylamino, heterocyclohydrocarbylsulfonylamino and N-  
5 monosubstituted or N,N-disubstituted aminohydrocarbyl group, wherein the substituent(s) on the nitrogen are selected from the group consisting of hydrocarbyl, aryl, arylhydrocarbyl, cyclohydrocarbyl, arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,  
10 and hydrocarboyl, or wherein the nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclic or heteroaryl ring group.

19. The compound or salt according to claim  
15 18 wherein said R<sup>1</sup> substituent is itself substituted with a substituent R<sup>4</sup> that is selected from the group consisting of one other single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl group, a C<sub>3</sub>-C<sub>14</sub> hydrocarbyl group, a C<sub>2</sub>-C<sub>14</sub>  
20 hydrocarbyloxy group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a nicotinamido group, an isonicotinamido group, a picolinamido group, an anilino group and a benzamido group.

25

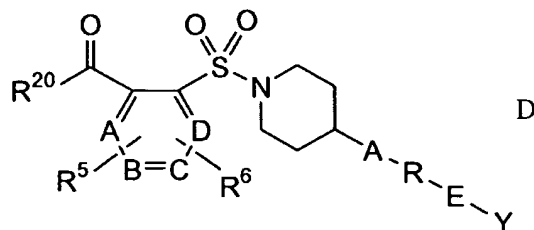
20. The compound or salt according to  
claim 19 wherein said R<sup>1</sup> substituent is PhR<sup>4</sup> in which Ph is phenyl substituted with R<sup>4</sup> at the 4-position, and said R<sup>4</sup> is selected from the group consisting of  
30 a phenyl, phenoxy, thiophenoxy, phenylazo, benzamido, anilino, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is optionally substituted

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at the meta- or para-position or both with a moiety that is selected from the group consisting of a halogen, a C<sub>1</sub>-C<sub>9</sub> hydrocarbyloxy group, a C<sub>1</sub>-C<sub>10</sub> hydrocarbyl group, a di- C<sub>1</sub>-C<sub>9</sub> hydrocarbylamino group, a carboxyl C<sub>1</sub>-C<sub>8</sub> hydrocarbyl group, a C<sub>1</sub>-C<sub>4</sub> hydrocarbyloxy carbonyl C<sub>1</sub>-C<sub>4</sub> hydrocarbyl group, a C<sub>1</sub>-C<sub>4</sub> hydrocarbyloxycarbonyl C<sub>1</sub>-C<sub>4</sub> hydrocarbyl group and a carboxamido C<sub>1</sub>-C<sub>8</sub> hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a methylenedioxy group.

21. The compound or salt according to claim 15 wherein said R<sup>1</sup> substituent has a length greater than that of an octyl group and less than that of a stearyl group.

22. A compound corresponding to Formula D, or a pharmaceutically acceptable salt thereof:



20

wherein

each of A, B, C and D is carbon, nitrogen, sulfur or oxygen that is present or absent so that the depicted ring has 5- or 6-members;

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy,

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haloalkyl, haloalkyloxy, hydroxyalkyl, a  
R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio,  
arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy,  
perfluoroalkyl, haloalkyl, heterocycloxy and a

5 R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent; and

or R<sup>5</sup> and R<sup>6</sup> together with the atoms to  
which they are bonded form a further aliphatic or  
aromatic carbocyclic or heterocyclic ring having 5-  
to 7-members;

10 in said -A-R-E-Y substituent, A is selected  
from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- 15 (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- 20 (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- 25 (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded  
30 to the depicted ring;

the moiety R is selected from the group  
consisting of alkyl, alkoxyalkyl, aryl, heteroaryl,



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cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the group E is selected from the group consisting of

- (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>R<sup>g</sup>- or -R<sup>g</sup>SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl, perfluoroalkoxy, perfluoroalkylthio,

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trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and an aminoalkyl group, wherein the aryl, heteroaryl, aralkyl or heterocycloalkyl group is (i) 5 unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, perfluoroalkyl, perfluoroalkoxy and an amino group 10 wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group; or

wherein  $R^a$  is selected from the group 15 consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl,  $R^bR^c$ aminoalkanoyl, haloalkanoyl,  $R^bR^c$ aminoalkyl, alkoxyalkyl, haloalkyl and an arylalkyloxy group;

$R^b$  and  $R^c$  are independently selected from 20 the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, 25 heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, 30 alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,

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heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
alkoxycarbonyl, aryloxy carbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
5 aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
10 group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
two or three groups independently selected from  $R^f$   
substituents;

15  $R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
arylalkylcarbonyl, alkoxy carbonyl and an  
arylalkyloxy carbonyl group; and

20  $R^f$  is selected from the group consisting of  
a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,  
cyano, and a  $R^d R^e$  amino group;

$R^g$  is selected from the group consisting of  
a hydrido, aryl, heteroaryl, heterocyclo, aroyl,  
25 alkanoyl, heteroaroyl, halogen cyano, aldehydo,  
hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl,  
cycloalkenyl, alkoxy, aryloxy, heteroaryloxy,  
alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  
 $R^h R^i$ -amino, alkoxyalkyl, alkylendioxy, aryloxyalkyl,  
30 perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio,  
alkyloxy carbonyl, alkyloxy carbonyloxy,  
aryloxy carbonyl, arylalkyloxy carbonyl,

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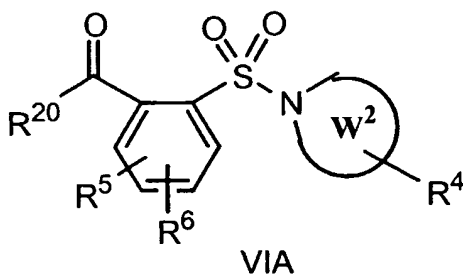
- arylalkyloxycarbonylamino, aryloxycarbonyloxy,  
carboxy,  $R^hR^i$ -aminocarbonyloxy,  $R^hR^i$ -aminocarbonyl,  
 $R^hR^i$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^hR^i$ -  
aminosulfonyl,  $R^hR^i$ -aminocarbonyl ( $R^h$ ) amino,  
5 trifluoromethyl-sulfonyl ( $R^h$ ) amino,  
heteroarylsulfonyl ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) amino,  
arylsulfonyl ( $R^h$ ) aminocarbonyl,  
alkylsulfonyl ( $R^h$ ) amino,  
arylcarbonyl ( $R^h$ ) aminosulfonyl, and an  
10 alkylsulfonyl ( $R^h$ ) aminocarbonyl substituent;  
 $R^h$  is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
15 alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
hydroxyalkyl group, each of which groups is  
optionally substituted by one or two groups  
20 independently selected from  $R^j$  substituents as are  
the substituents of the substituted aminoalkyl and  
substituted aminoalkanoyl groups;  
 $R^i$  is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
25 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
30 hydroxyalkyl group, each of which groups are  
optionally substituted by one or two  $R^j$  substituents;

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wherein  $R^j$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

$R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,  $R^d$ amino carbonyl,  $R^d$ aminosulfonyl,  $R^d$ aminoalkanoyl and  $R^d$ aminoalkysulfonyl.

23. A compound corresponding to Formula VIA, or a pharmaceutically acceptable salt thereof:



wherein:

$R^4$  is a substituent that has a chain length of 3 to about 14 carbon atoms;

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ring structure  $W^2$  including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 6-members, and  $R^4$  is a substituent bonded at the 4-position relative to that depicted nitrogen atom.

5 when  $W^2$  is a 6-membered ring and at the 3- or 4-position relative to that depicted nitrogen when  $W^2$  is a 5-membered ring;

$R^5$  and  $R^6$  are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a  $R^bR^c$ aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a  $R^bR^c$ aminoalkyloxy substituent;

or  $R^5$  and  $R^6$  together with the atoms to which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members; and

20  $R^{20}$  is (a)  $-O-R^{21}$ , where  $R^{21}$  is selected from the group consisting of a hydrido,  $C_1$ - $C_6$ -alkyl, aryl, ar- $C_1$ - $C_6$ -alkyl group and a pharmaceutically acceptable cation, (b)  $-NR^{13}-O-R^{22}$  wherein  $R^{22}$  is a selectively removable protecting group and  $R^{13}$  is a hydrido,  $C_1$ - $C_6$ -alkyl or benzyl group, (c)  $-NR^{13}-O-R^{14}$ , where  $R^{13}$  is as before and  $R^{14}$  is hydrido, a pharmaceutically acceptable cation or  $C(V)R^{15}$  where V is O or S and  $R^{15}$  is selected from the group consisting of an  $C_1$ - $C_6$ -alkyl, aryl,  $C_1$ - $C_6$ -alkoxy, heteroaryl- $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_8$ -cycloalkyl- $C_1$ - $C_6$ -alkyl,

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aryloxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxy, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, heteroaryl and amino C<sub>1</sub>-C<sub>6</sub>-alkyl group wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents

5 independently selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, and C<sub>1</sub>-C<sub>6</sub>-alkanoyl radical, or

10 (iii) wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) -NR<sup>23</sup>R<sup>24</sup>, where R<sup>23</sup> and R<sup>24</sup> are independently selected from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, amino C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, and an ar-C<sub>1</sub>-C<sub>6</sub>-

15 alkyl group, or R<sup>23</sup> and R<sup>24</sup> together with the depicted nitrogen atom form a 5- to 8-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur;

wherein R<sup>b</sup> and R<sup>c</sup> are independently

20 selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl,

25 heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl,

30 alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl,

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heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
5 alkoxy carbonyl, aryloxy carbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
10 amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
15 two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
20 arylalkylcarbonyl, alkoxy carbonyl and an  
arylalkyloxy carbonyl group; and

$R^f$  is selected from the group consisting of  
a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,  
cyano, and a  $R^d R^e$  amino group.

25

24. The compound or salt according to  
claim 23 wherein said  $R^4$  substituent is selected from  
the group consisting of a phenyl group, a phenoxy  
group, a thiophenoxy group, an anilino group, a  
30 phenylazo group, a phenylureido, a benzamido, a  
nicotinamido, an isonicotinamido, a picolinamido  
group, a heterocyclo, heterocyclohydrocarbyl,



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arylheterocyclohydrocarbyl, arylhydrocarbyl,  
heteroarylhydrocarbyl, heteroarylheterocyclo-  
hydrocarbyl, arylhydrocarbyloxyhydrocarbyl,  
aryloxyhydrocarbyl, hydrocarboylhydrocarbyl,  
5 arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl,  
arylazoaryl, arylhydrazinoaryl, hydrocarbylthio-  
hydrocarbyl, hydrocarbylthioaryl, arylthio-  
hydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbyl-  
thioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl,  
10 arylhydrocarbylthioaryl, arylhydrocarbylamino,  
heteroarylhydrocarbylamino, and a heteroarylthio  
group.

25. The compound or salt according to  
15 claim 24 wherein said R<sup>4</sup> substituent is itself  
substituted by one or more substituents selected from  
the group consisting of a halogen, hydrocarbyl,  
hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl,  
trifluoromethyl-hydrocarbyl, hydroxy, mercapto,  
20 hydroxycarbonyl, aryloxy, arylthio, arylamino,  
arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio,  
heteroarylamino, heteroarhydrocarbyl,  
hydrocarbyloxycarbonyl-hydrocarbyl, heterocyclooxy,  
hydroxycarbonyl-hydrocarbyl, heterocyclothio,  
25 heterocycloamino, cyclohydrocarbyloxy,  
cyclohydrocarbylthio, cyclohydrocarbylamino,  
heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio,  
heteroarylhydrocarbyl-amino, arylhydrocarbyloxy,  
arylhydrocarbylthio, arylhydrocarbylamino,  
30 heterocyclic, heteroaryl, hydroxycarbonyl-  
hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl,  
arylcarbonyl, arylhydrocarbyloyl, hydrocarboylloxy,  
arylhydrocarboylloxy, hydroxyhydrocarbyl,

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hydroxyhydrocarbyloxy, hydrocarbylthio,  
hydrocarbyloxyhydrocarbylthio,  
hydrocarbyloxycarbonyl, hydroxycarbonyl-  
hydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl,  
5 hydrocarbylhydroxycarbonyl-hydrocarbylthio,  
hydrocarbyloxycarbonylhydrocarbyloxy,  
hydrocarbyloxycarbonylhydrocarbylthio, amino,  
hydrocarbylcarbonylamino, arylcarbonylamino,  
cyclohydrocarbylcarbonylamino, heterocyclo-  
10 hydrocarbylcarbonylamino, arylhydrocarbyl-  
carbonylamino, heteroarylcarbonylamino,  
heteroarylhydrocarbylcarbonylamino,  
heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,  
arylsulfonylamino, arylhydrocarbylsulfonylamino,  
15 heteroarylsulfonylamino, heteroarylhydrocarbyl-  
sulfonylamino, cyclohydrocarbylsulfonylamino,  
heterocyclohydrocarbylsulfonylamino and N-  
monosubstituted or N,N-disubstituted aminohydrocarbyl  
group, wherein the substituent(s) on the nitrogen are  
20 selected from the group consisting of hydrocarbyl,  
aryl, arylhydrocarbyl, cyclohydrocarbyl,  
arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,  
and hydrocarboyl, or wherein the nitrogen and two  
substituents attached thereto form a 5- to 8-membered  
25 heterocyclic or heteroaryl ring group.

26. The compound or salt according to  
claim 23 wherein said R<sup>20</sup> is -NR<sup>13</sup>-O-R<sup>14</sup>.

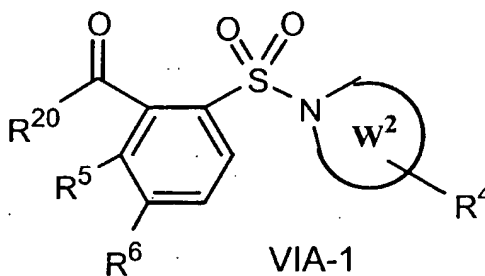
30 27. The compound or salt according to  
claim 26 wherein said R<sup>13</sup> is hydrido.

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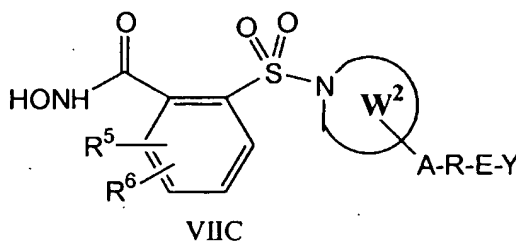
28. The compound or salt according to claim 23 wherein said R<sup>20</sup> is -NR<sup>13</sup>-O-R<sup>22</sup>.

29. The compound or salt according to claim 28 wherein said R<sup>13</sup> is hydrido and said R<sup>22</sup> is selected from the group consisting of a 2-tetrahydropyranyl, benzyl, p-methoxybenzyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, trisubstituted silyl group, o-nitrophenyl group, and a peptide synthesis resin, wherein said trisubstituted silyl group is substituted with a C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, or ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group or a mixture thereof.

30. The compound or salt according to claim 23 wherein the compound corresponds in structure to Formula VIA-1



31. A compound corresponding to Formula VIIC, or a pharmaceutically acceptable salt thereof:



wherein:

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$R^5$  and  $R^6$  are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a

5  $R^bR^c$ aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a  $R^bR^c$ aminoalkyloxy substituent; and

or  $R^5$  and  $R^6$  together with the atoms to  
10 which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members;

ring structure  $W^2$  including the depicted nitrogen atom is a heterocyclic ring that contains 5-  
15 or 6-members, and the substituent -A-R-E-Y is bonded at the 4-position relative to that depicted nitrogen atom when  $W^2$  is a 6-membered ring and at the 3- or 4-position relative to that depicted nitrogen when  $W^2$  is a 5-membered ring;

20 in said -A-R-E-Y substituent, A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- 25 (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- 30 (9) -C≡C-;
- (10) -N=N-;

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- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- 5 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to ring structure W<sup>2</sup>;

10 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,

15 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted

20 with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,

25 hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the group E is selected from the group consisting of

- 30 (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;

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(4)  $-\text{SO}_2\text{R}^g-$  or  $-\text{R}^g\text{SO}_2-$ ;

(5)  $-\text{SO}_2-$ ;

(6)  $-\text{N}(\text{R}^k)-\text{SO}_2-$  or  $-\text{SO}_2-\text{N}(\text{R}^k)-$ ; or

(7) E is absent and R is bonded directly to Y; and

5

the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy,

10 heteroaryloxy, heteroaralkyl,  $\text{R}^a\text{oxyalkyl}$ ,

perfluoroalkoxy, perfluoroalkylthio,

trifluoromethylalkyl, alkenyl, heterocycloalkyl,

cycloalkyl, trifluoromethyl, alkoxy carbonyl, and a

aminoalkyl group, wherein the aryl, heteroaryl,

15 aralkyl or heterocycloalkyl group is (i)

unsubstituted or (ii) substituted with one or two

radicals independently selected from the group

consisting of an alkanoyl, halo, nitro, nitrile,

haloalkyl, alkyl, aralkyl, aryl, alkoxy,

20 perfluoroalkyl, perfluoroalkoxy and an amino group

wherein the amino nitrogen is (i) unsubstituted or

(ii) substituted with one or two groups independently

selected from hydrido, alkyl, and an aralkyl group;

wherein

25  $\text{R}^a$  is selected from the group consisting of

a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl,

alkanoyl, aroyl, arylalkylcarbonyl,  $\text{R}^b\text{R}^c\text{aminoalkanoyl}$ ,

haloalkanoyl,  $\text{R}^b\text{R}^c\text{aminoalkyl}$ , alkoxyalkyl, haloalkyl

and an arylalkyloxy group;

30  $\text{R}^b$  and  $\text{R}^c$  are independently selected from

the group consisting of a hydrido, alkanoyl,

arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl,

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perfluoroalkyl, trifluoromethylalkyl,  
perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl,  
heterocycloalkyl, heterocycloalkylcarbonyl, aryl,  
heterocyclo, heteroaryl, cycloalkylalkyl,  
5 aryloxyalkyl, heteroaryloxyalkyl,  
heteroarylalkoxyalkyl, heteroarylthioalkyl,  
arylsulfonyl, aralkanoyl, alkylsulfonyl,  
heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
10 alkyliminocarbonyl, aryliminocarbonyl,  
heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
15 alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
20 amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
25 two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
30 arylalkylcarbonyl, alkoxycarbonyl and an  
arylalkyloxycarbonyl group;

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$R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen, aryl, alkoxy, cyano, and a  $R^{dRe}$  amino group;

$R^g$  is selected from the group consisting of

5 a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,

10  $R^{hRi}$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy,

15 carboxy,  $R^{hRi}$ -aminocarbonyloxy,  $R^{hRi}$ -aminocarbonyl,  $R^{hRi}$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^{hRi}$ -aminosulfonyl,  $R^{hRi}$ -aminocarbonyl( $R^h$ )amino, trifluoromethylsulfonyl( $R^h$ )amino, heteroarylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )amino, arylsulfonyl( $R^h$ )-

20 aminocarbonyl, alkylsulfonyl( $R^h$ )amino, arylcarbonyl- ( $R^h$ )aminosulfonyl, and an alkylsulfonyl( $R^h$ )-aminocarbonyl substituent;

$R^h$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,

25 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a

30 hydroxyalkyl group, each of which groups is optionally substituted by one or two groups



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independently selected from R<sup>j</sup> substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

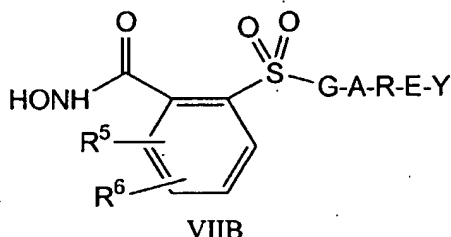
R<sup>i</sup> is selected from the group consisting of  
5 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or  
10 unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two R<sup>j</sup> substituents;

wherein R<sup>j</sup> is selected from the group consisting of an arylalkyl, aryl, heteroaryl,  
15 heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a  
20 hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an  
25 alkyloxycarbonyl group; and

R<sup>k</sup> is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R<sup>C</sup>R<sup>d</sup>amino carbonyl, R<sup>C</sup>R<sup>d</sup>aminosulfonyl,  
30 R<sup>C</sup>R<sup>d</sup>aminoalkanoyl and R<sup>C</sup>R<sup>d</sup>aminoalkysulfonyl.

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32. A compound corresponding to Formula VIIB, or a pharmaceutically acceptable salt thereof:



5 wherein:

$R^5$  and  $R^6$  are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a  
 10  $R^{bR^c}$ aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocyclooxy and a  $R^{bR^c}$ aminoalkyloxy substituent; and

or  $R^5$  and  $R^6$  together with the atoms to  
 15 which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members;

G is a N-heterocyclo group;

the substituent A is selected from the  
 20 group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- 25 (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;

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- (9)  $-C\equiv C-$ ;  
 (10)  $-N=N-$ ;  
 (11)  $-NH-NH-$ ;  
 (12)  $-CS-N(R^k)-$  or  $-N(R^k)-CS-$ ;  
 5 (13)  $-CH_2-$ ;  
 (14)  $-O-CH_2-$  or  $-CH_2-O-$ ;  
 (15)  $-S-CH_2-$  or  $-CH_2-S-$ ;  
 (16)  $-SO-$ ; and  
 (17)  $-SO_2-$ ; or  
 10 (18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, 15 heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or 20 heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, 25 trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy,  $C_1-C_2$ -alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

30 the moiety E is selected from the group consisting of

- (1)  $-COR^g-$  or  $-R^gCO-$ ;

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- (2)  $-\text{CON}(\text{R}^k)-$  or  $-(\text{R}^k)\text{NCO}-$ ;
- (3)  $-\text{CO}-$ ;
- (4)  $-\text{SO}_2-\text{R}^g-$  or  $-\text{R}^g-\text{SO}_2-$ ;
- (5)  $-\text{SO}_2-$ ;
- 5 (6)  $-\text{N}(\text{R}^k)-\text{SO}_2-$  or  $-\text{SO}_2-\text{N}(\text{R}^k)-$ ; or
- (7) E is absent and R is bonded directly to Y; and
- the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl,  $\text{R}^a\text{oxyalkyl}$ , perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a
- 10 aminoalkyl group, wherein the aryl, heteroaryl, aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy perfluoroalkyl, perfluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently
- 20 selected from hydrido, alkyl, and an aralkyl group; wherein
- $\text{R}^a$  is selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl,  $\text{R}^b\text{RCaminoalkanoyl}$ , haloalkanoyl,  $\text{R}^b\text{RCaminoalkyl}$ , alkoxyalkyl, haloalkyl
- 30 and an arylalkyloxy group;

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- $R^b$  and  $R^c$  are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl,
- 5 perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl,
- 10 arylsulfonyl, aralkanoyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, , alkoxy-carbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl,
- 15 alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl, thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy-carbonyl, aryloxy-carbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,
- 20 aminosulfonyl wherein the amino nitrogen is (i) unsubstituted or (ii) independently substituted with one or two  $R^d$  radicals, or the substituents on the amino group taken together with the amino nitrogen form a saturated or partially unsaturated heterocyclo
- 25 group optionally substituted with one, two or three groups independently selected from  $R^d$  substituents or a heteroaryl group optionally substituted with one, two or three groups independently selected from  $R^f$  substituents;
- 30  $R^d$  and  $R^e$  are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl,

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arylalkylcarbonyl, alkoxycarbonyl and an  
arylalkyloxycarbonyl group;

$R^f$  is selected from the group consisting of  
a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,

5 cyano, and a  $R^d R^e$  amino group;

$R^g$  is selected from the group consisting of  
a hydrido, aryl, heteroaryl, heterocyclo, aroyl,  
alkanoyl, heteroaroyl, halogen cyano, aldehydo,  
hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl,  
10 cycloalkenyl, alkoxy, aryloxy, heteroaryloxy,  
alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  
 $R^{hR^i}$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl,  
perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio,  
alkyloxycarbonyl, alkyloxycarbonyloxy,  
15 aryloxycarbonyl, arylalkyloxycarbonyl,  
arylalkyloxycarbonylamino, aryloxycarbonyloxy,  
carboxy,  $R^{hR^i}$ -aminocarbonyloxy,  $R^{hR^i}$ -aminocarbonyl,  
 $R^{hR^i}$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^{hR^i}$ -  
aminosulfonyl,  $R^{hR^i}$ -aminocarbonyl ( $R^h$ ) amino,  
20 trifluoromethyl-sulfonyl ( $R^h$ ) amino,  
heteroarylsulfonyl ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) amino,  
arylsulfonyl ( $R^h$ ) aminocarbonyl,  
alkylsulfonyl ( $R^h$ ) amino,  
arylcarbonyl ( $R^h$ ) aminosulfonyl, and an  
25 alkylsulfonyl ( $R^h$ ) aminocarbonyl substituent;

$R^h$  is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
30 alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or

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unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is optionally substituted by one or two groups independently selected from  $R^j$  substituents as are  
5 the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

$R^i$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl,  
10 substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are  
15 optionally substituted by one or two  $R^j$  substituents;

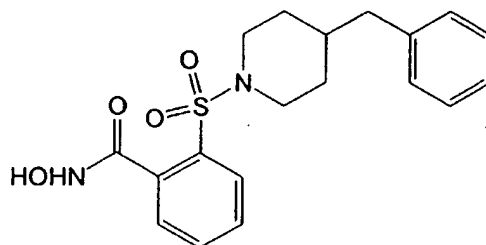
$R^j$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl,  
20 alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl  
25 groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

$R^k$  is selected from hydrido, alkyl, alkenyl,  
30 alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,

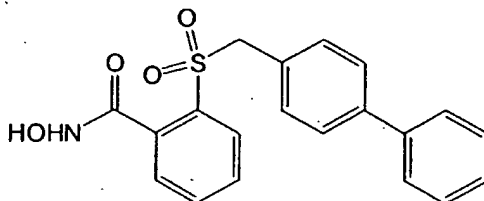
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$R^C R^d$ amino carbonyl,  $R^C R^d$ aminosulfonyl,  
 $R^C R^d$ aminoalkanoyl and  $R^C R^d$ aminoalkysulfonyl.

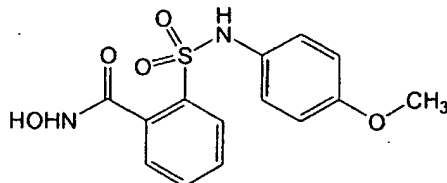
33. The compound or salt according to  
5 claim 32 wherein the compound corresponds to the  
formula



34. The compound or salt according to  
10 claim 32 wherein the compound corresponds to the  
formula



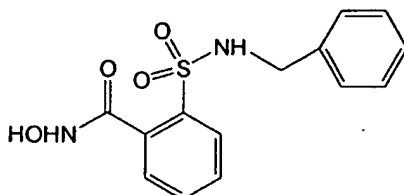
35. The compound or salt according to  
claim 32 wherein the compound corresponds to the  
15 formula



36. The compound or salt according to  
claim 32 wherein the compound corresponds to the  
formula

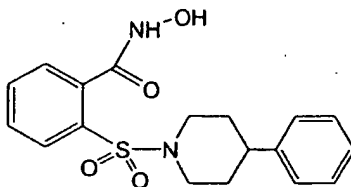


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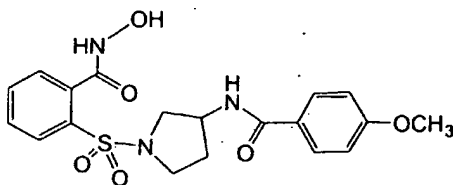
37. The compound or salt according to claim 32 wherein the compound corresponds to the formula

5



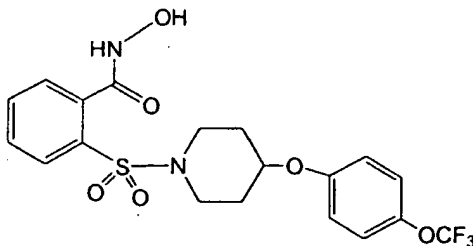
38. The compound or salt according to claim 32 wherein the compound corresponds to the formula

10



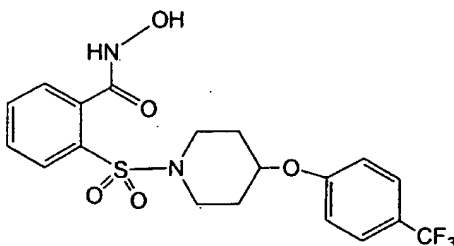
39. The compound or salt according to claim 32 wherein the compound corresponds to the formula

15



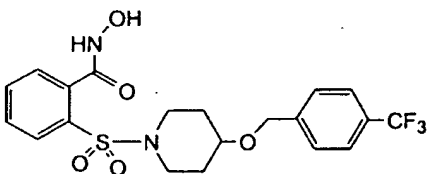
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40. The compound or salt according to claim 32 wherein the compound corresponds to the formula



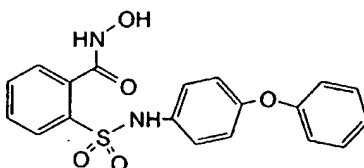
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41. The compound or salt according to claim 32 wherein the compound corresponds to the formula



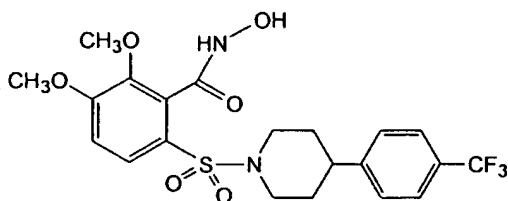
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42. The compound or salt according to claim 32 wherein the compound corresponds to the formula



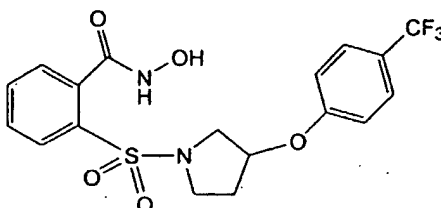
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43. The compound or salt according to claim 32 wherein the compound corresponds to the formula

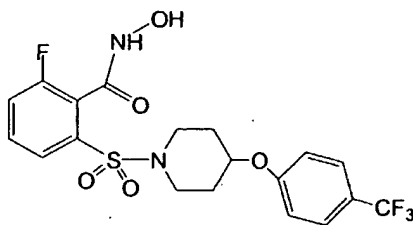


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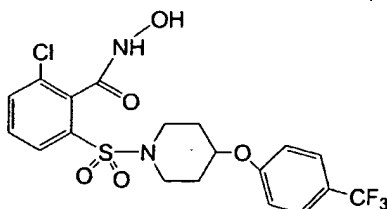
44. The compound or salt according to claim 32 wherein the compound corresponds to the formula



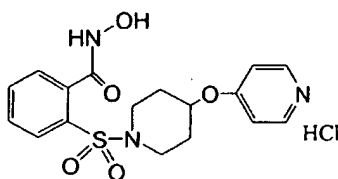
5 45. The compound or salt according to claim 32 wherein the compound corresponds to the formula



46. The compound or salt according to claim 32 wherein the compound corresponds to the formula

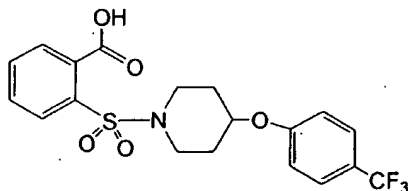


47. The compound or salt according to claim 32 wherein the compound\* corresponds to the formula

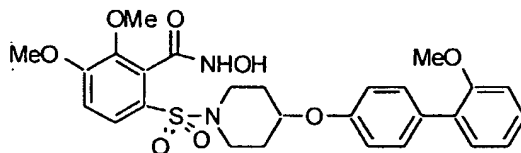


-326-

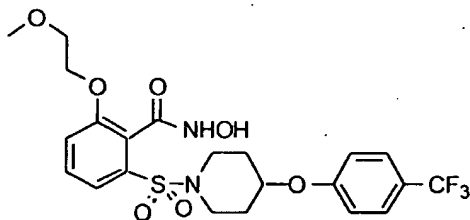
48. The compound or salt according to claim 32 wherein the compound corresponds to the formula



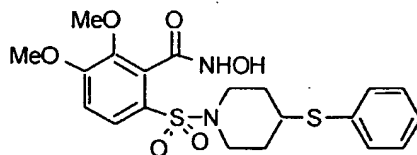
5 49. The compound or salt according to claim 32 wherein the compound corresponds to the formula



10 50. The compound or salt according to claim 32 wherein the compound corresponds to the formula

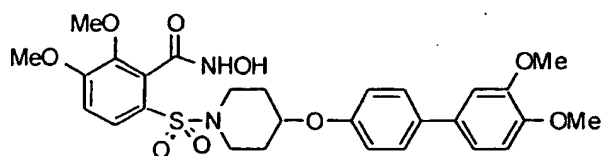


15 51. The compound or salt according to claim 32 wherein the compound corresponds to the formula

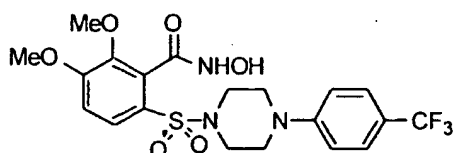


52. The compound or salt according to claim 32 wherein the compound corresponds to the formula

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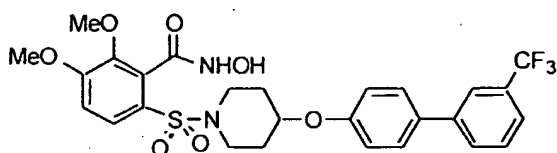


53. The compound or salt according to claim 32 wherein the compound corresponds to the formula



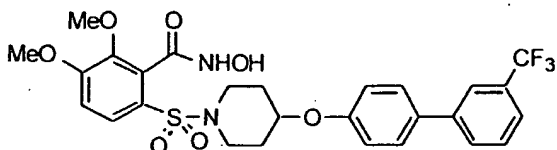
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54. The compound or salt according to claim 32 wherein the compound corresponds to the formula



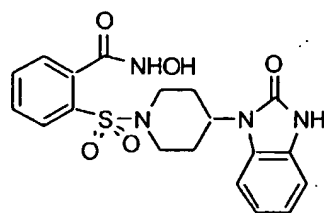
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55. The compound or salt according to claim 32 wherein the compound corresponds to the formula



15

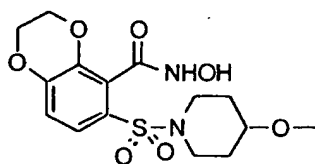
56. The compound or salt according to claim 32 wherein the compound corresponds to the formula



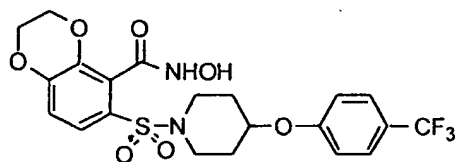
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57. The compound or salt according to claim 32 wherein the compound corresponds to the formula

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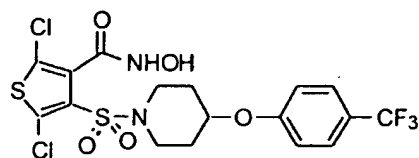


58. The compound or salt according to claim 32 wherein the compound corresponds to the formula



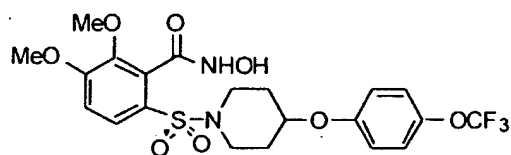
5

59. The compound or salt according to claim 32 wherein the compound corresponds to the formula

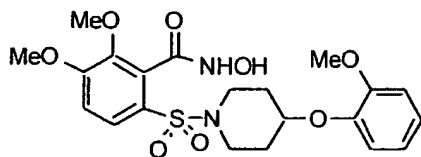


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60. The compound or salt according to claim 32 wherein the compound corresponds to the formula



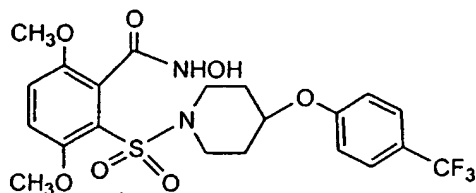
61. The compound or salt according to claim 32 wherein the compound corresponds to the formula



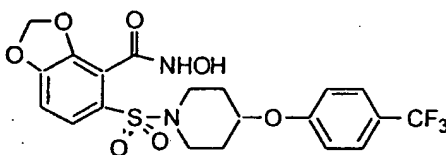
62. The compound or salt according to claim 32 wherein the compound corresponds to the formula

20

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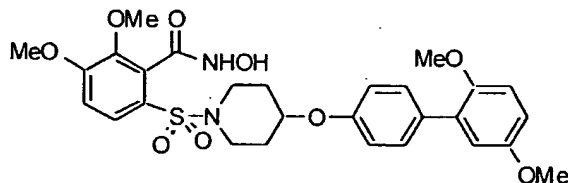


63. The compound or salt according to claim 32 wherein the compound corresponds to the formula



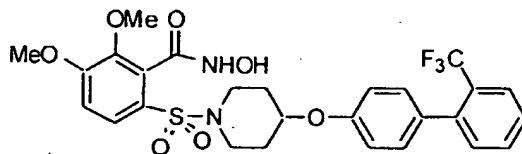
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64. The compound or salt according to claim 32 wherein the compound corresponds to the formula

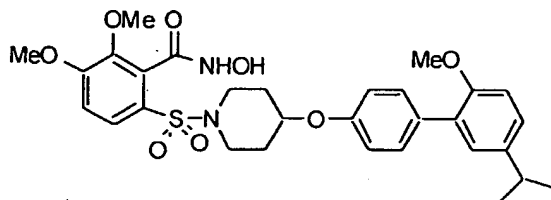


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65. The compound or salt according to claim 32 wherein the compound corresponds to the formula



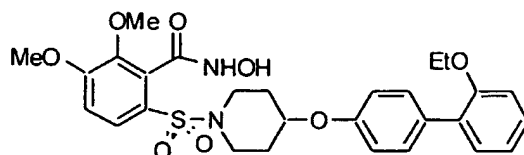
66. The compound or salt according to claim 32 wherein the compound corresponds to the formula



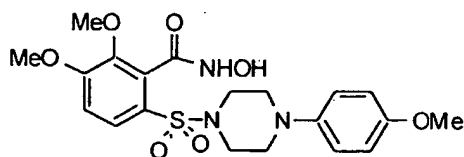
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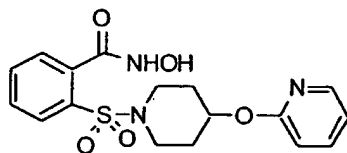
67. The compound or salt according to claim 32 wherein the compound corresponds to the formula



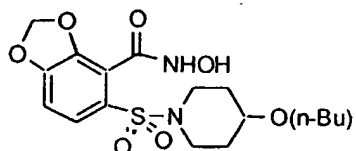
5 68. The compound or salt according to claim 32 wherein the compound corresponds to the formula



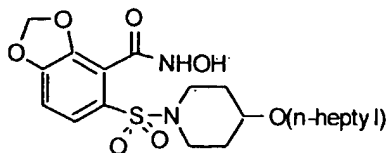
10 69. The compound or salt according to claim 32 wherein the compound corresponds to the formula



15 70. The compound or salt according to claim 32 wherein the compound corresponds to the formula



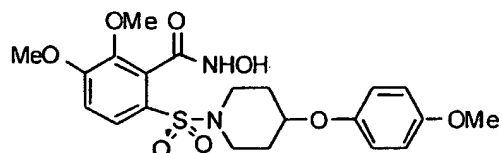
71. The compound or salt according to claim 32 wherein the compound corresponds to the formula



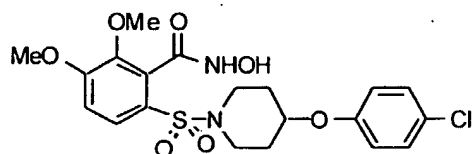


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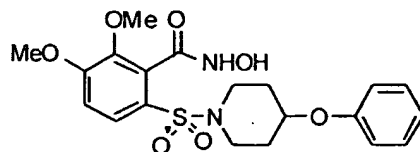
72. The compound or salt according to claim 32 wherein the compound corresponds to the formula



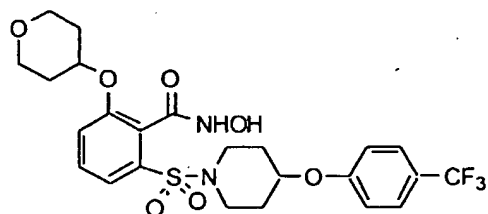
5 73. The compound or salt according to claim 32 wherein the compound corresponds to the formula



10 74. The compound or salt according to claim 32 wherein the compound corresponds to the formula

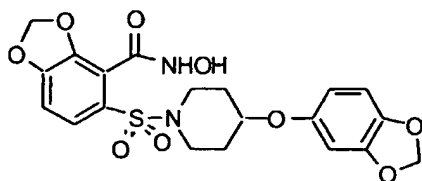


15 75. The compound or salt according to claim 32 wherein the compound corresponds to the formula

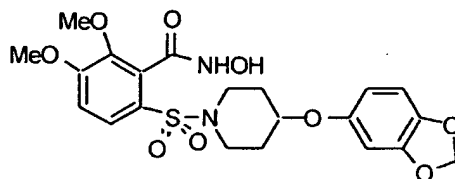


76. The compound or salt according to claim 32 wherein the compound corresponds to the formula

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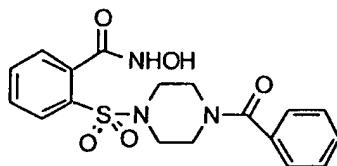


77. The compound or salt according to claim 32 wherein the compound corresponds to the formula



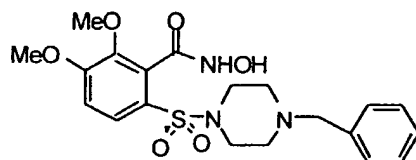
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78. The compound or salt according to claim 32 wherein the compound corresponds to the formula

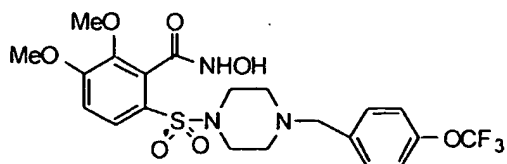


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79. The compound or salt according to claim 32 wherein the compound corresponds to the formula



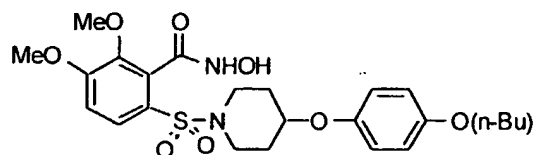
80. The compound or salt according to claim 32 wherein the compound corresponds to the formula



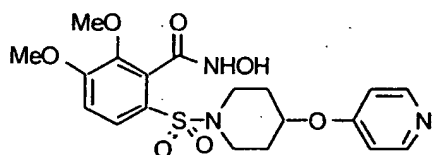
15

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81. The compound or salt according to claim 32 wherein the compound corresponds to the formula

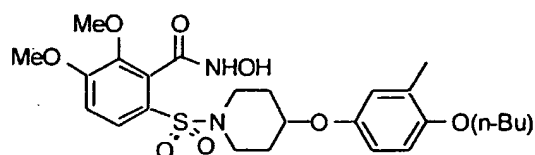


5 82. The compound or salt according to claim 32 wherein the compound corresponds to the formula

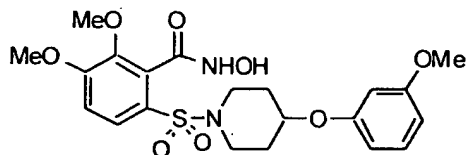


10 83. The compound or salt according to claim 32 wherein the compound corresponds to the formula

15 84. The compound or salt according to claim 32 wherein the compound corresponds to the formula



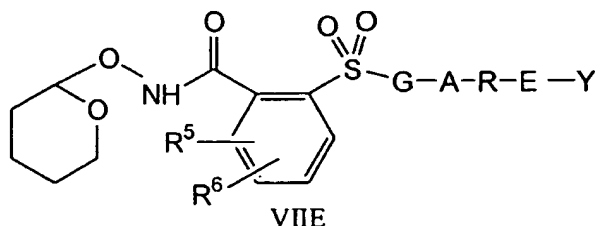
85. The compound or salt according to claim 32 wherein the compound corresponds to the formula



20

86. A compound corresponding to Formula VIIE, or a pharmaceutically acceptable salt thereof:

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wherein:

$R^5$  and  $R^6$  are independently selected from

5 the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a  $R^b R^c$  aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkkoxy, alkoxyalkoxy,

10 perfluoroalkyl, haloalkyl, heterocyclooxy and a  $R^b R^c$  aminoalkyloxy substituent; and

or  $R^5$  and  $R^6$  together with the atoms to which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5-

15 to 7-members;

G is a N-heterocyclo group;

the substituent A is selected from the group consisting of

- (1) -O-;
- 20 (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- 25 (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -N=N-;

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- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- 5 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to the N-heterocyclo group, G;
- 10 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,
- 15 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted
- 20 with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,
- 25 hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the moiety E is selected from the group consisting of

- 30 (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;

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(4)  $-\text{SO}_2-\text{R}^g-$  or  $-\text{R}^g-\text{SO}_2-$ ;(5)  $-\text{SO}_2-$ ;(6)  $-\text{N}(\text{R}^k)-\text{SO}_2-$  or  $-\text{SO}_2-\text{N}(\text{R}^k)-$ ; or

(7) E is absent and R is bonded directly to Y; and

5

the moiety Y is absent or is selected from

the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy,

10 heteroaryloxy, heteroaralkyl,  $\text{R}^a$ oxyalkyl,

perfluoroalkoxy, perfluoroalkylthio,

trifluoromethylalkyl, alkenyl, heterocycloalkyl,

cycloalkyl, trifluoromethyl, alkoxy carbonyl, and a

aminoalkyl group, wherein the aryl, heteroaryl,

15 aralkyl or heterocycloalkyl group is (i)

unsubstituted or (ii) substituted with one or two

radicals independently selected from the group

consisting of an alkanoyl, halo, nitro, nitrile,

haloalkyl, alkyl, aralkyl, aryl, alkoxy,

20 perfluoroalkyl, perfluoroalkoxy and an amino group

wherein the amino nitrogen is (i) unsubstituted or

(ii) substituted with one or two groups independently

selected from hydrido, alkyl, and an aralkyl group;

wherein

25

 $\text{R}^a$  is selected from the group consisting of

a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl,

alkanoyl, aroyl, arylalkylcarbonyl,  $\text{R}^b\text{R}^c$ aminoalkanoyl,haloalkanoyl,  $\text{R}^b\text{R}^c$ aminoalkyl, alkoxyalkyl, haloalkyl

and an arylalkyloxy group;

30

 $\text{R}^b$  and  $\text{R}^c$  are independently selected from

the group consisting of a hydrido, alkanoyl,

arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl,

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- perfluoroalkyl, trifluoromethylalkyl,  
perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl,  
heterocycloalkyl, heterocycloalkylcarbonyl, aryl,  
heterocyclo, heteroaryl, cycloalkylalkyl,  
5 aryloxyalkyl, heteroaryloxyalkyl,  
heteroarylalkoxyalkyl, heteroarylthioalkyl,  
arylsulfonyl, aralkanoyl, alkylsulfonyl,  
heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
10 alkyliminocarbonyl, aryliminocarbonyl,  
heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
15 alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
20 amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
25 two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
30 arylalkylcarbonyl, alkoxycarbonyl and an  
arylalkyloxycarbonyl group;

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$R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen, aryl, alkoxy, cyano, and a  $R^{dR^e}$  amino group;

$R^g$  is selected from the group consisting of

5 a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,

10  $R^{hR^i}$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy,

15 carboxy,  $R^{hR^i}$ -aminocarbonyloxy,  $R^{hR^i}$ -aminocarbonyl,  $R^{hR^i}$ -aminoalkanoyl, hydroxyaminocarbonyl,  $R^{hR^i}$ -aminosulfonyl,  $R^{hR^i}$ -aminocarbonyl ( $R^h$ ) amino, trifluoromethyl-sulfonyl ( $R^h$ ) amino, heteroarylsulfonyl ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) amino,

20 arylsulfonyl ( $R^h$ ) aminocarbonyl, alkylsulfonyl ( $R^h$ ) amino, arylcarbonyl ( $R^h$ ) aminosulfonyl, and an alkylsulfonyl ( $R^h$ ) aminocarbonyl substituent;

$R^h$  is selected from the group consisting of

25 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or

30 unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is



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optionally substituted by one or two groups independently selected from  $R^j$  substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

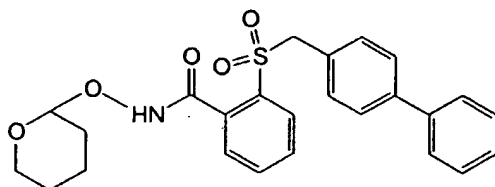
5  $R^i$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, 10 haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two  $R^j$  substituents;

$R^j$  is selected from the group consisting of 15 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or 20 unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, 25 heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

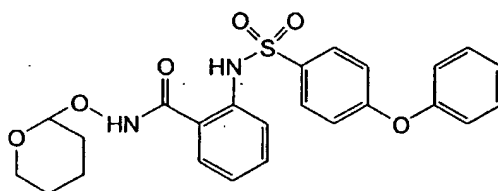
$R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, 30  $R^{CR^d}$ amino carbonyl,  $R^{CR^d}$ aminosulfonyl,  $R^{CR^d}$ aminoalkanoyl and  $R^{CR^d}$ aminoalkylsulfonyl.

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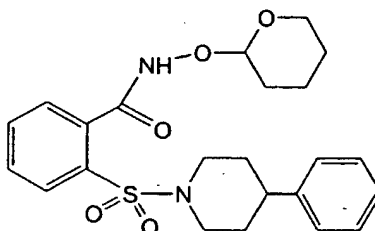
87. The compound according to claim 86  
wherein the compound corresponds to the formula



88. The compound according to claim 86  
5 wherein the compound corresponds to the formula

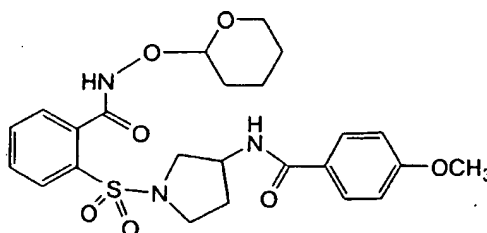


89. The compound according to claim 86  
wherein the compound corresponds to the formula



10

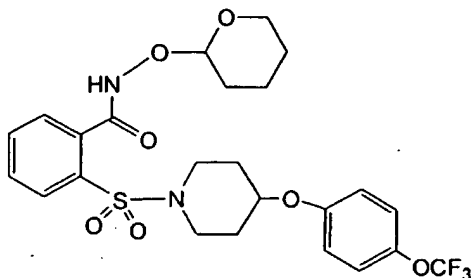
90. The compound according to claim 86  
wherein the compound corresponds to the formula



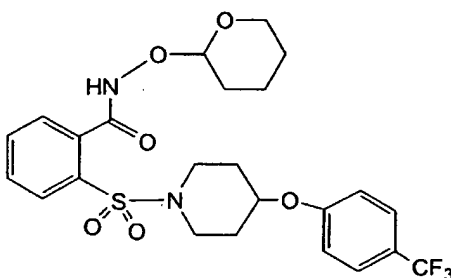
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91. The compound according to claim 86  
wherein the compound corresponds to the formula

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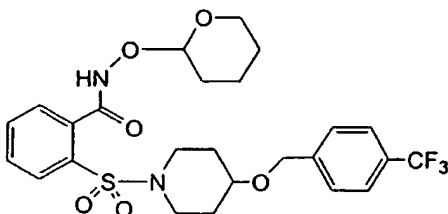


92. The compound according to claim 86  
wherein the compound corresponds to the formula

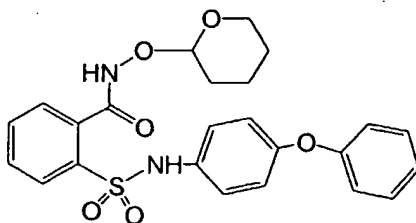


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93. The compound according to claim 86  
wherein the compound corresponds to the formula

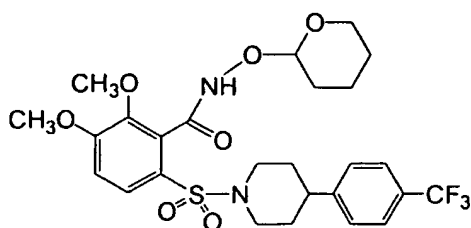


94. The compound according to claim 86  
10 wherein the compound corresponds to the formula

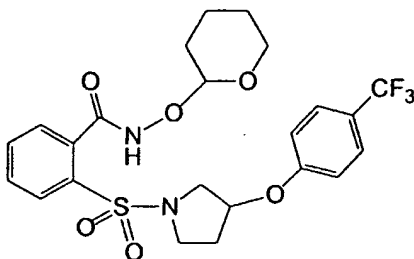


95. The compound according to claim 86  
wherein the compound corresponds to the formula

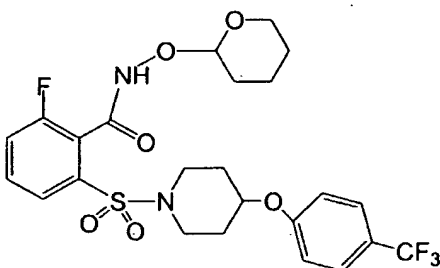
-342-



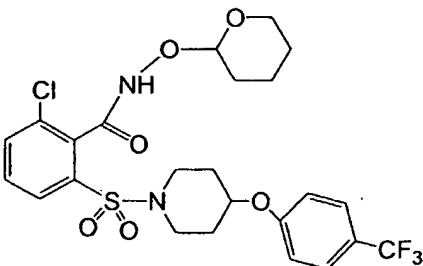
96. The compound according to claim 86  
wherein the compound corresponds to the formula



5 97. The compound according to claim 86  
wherein the compound corresponds to the formula



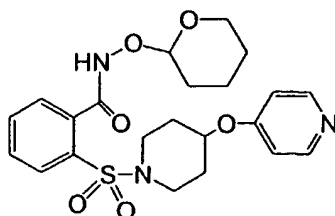
98. The compound according to claim 86  
wherein the compound corresponds to the formula



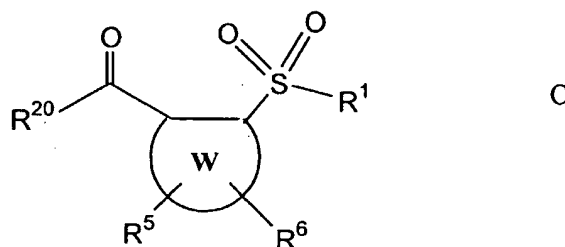
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99. The compound according to claim 86  
wherein the compound corresponds to the formula

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100. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that comprises
- 5 administering a compound corresponding in structure to Formula C or a pharmaceutically acceptable salt thereof in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition:



10

wherein

the ring structure W is a 5- or 6-membered aromatic or heteroaromatic ring;

- 15  $R^1$  is (i) a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical that is bonded directly to the depicted  $SO_2$ -group and having a length greater than about that of a hexyl group and less than about that
- 20 of an eicosyl group, said  $R^1$  defining a three-dimensional volume, when rotated about an axis drawn through the  $SO_2$ -bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the  $SO_2$ -bonded 1-position and the center of 3,4-bond of a

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5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings;

5                     $R^5$  and  $R^6$  are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a  $R^{bRC}$ aminoalkyl substituent, thiol, alkylthio, 10 arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a  $R^{bRC}$ aminoalkyloxy substituent;

                  or  $R^5$  and  $R^6$  together with the atoms to which they are bonded form a further aliphatic or 15 aromatic carbocyclic or heterocyclic ring having 5- to 7-members; and

$R^{20}$  is (a)  $-O-R^{21}$ , where  $R^{21}$  is selected from the group consisting of a hydrido,  $C_1$ - $C_6$ -alkyl, aryl, ar- $C_1$ - $C_6$ -alkyl group and a pharmaceutically 20 acceptable cation, (b)  $-NR^{13}-O-R^{22}$  wherein  $R^{22}$  is a selectively removable protecting group and  $R^{13}$  is a hydrido,  $C_1$ - $C_6$ -alkyl or benzyl group, (c)  $-NR^{13}-O-R^{14}$ , where  $R^{13}$  is as before and  $R^{14}$  is hydrido, a pharmaceutically acceptable cation or  $C(V)R^{15}$  where V 25 is O or S and  $R^{15}$  is selected from the group consisting of an  $C_1$ - $C_6$ -alkyl, aryl,  $C_1$ - $C_6$ -alkoxy, heteroaryl- $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_8$ -cycloalkyl- $C_1$ - $C_6$ -alkyl, aryloxy, ar- $C_1$ - $C_6$ -alkoxy, ar- $C_1$ - $C_6$ -alkyl, heteroaryl and amino  $C_1$ - $C_6$ -alkyl group wherein the amino  $C_1$ - $C_6$ - 30 alkyl nitrogen is (i) unsubstituted or (ii)

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substituted with one or two substituents independently selected from the group consisting of an C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, ar-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, ar-C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, and C<sub>1</sub>-C<sub>6</sub>-alkanoyl radical, or (iii) wherein the amino C<sub>1</sub>-C<sub>6</sub>-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) -NR<sup>23</sup>R<sup>24</sup>, where R<sup>23</sup> and R<sup>24</sup> are independently selected from the group consisting of a hydrido, C<sub>1</sub>-C<sub>6</sub>-alkyl, amino C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, and an ar-C<sub>1</sub>-C<sub>6</sub>-alkyl group, or R<sup>23</sup> and R<sup>24</sup> together with the depicted nitrogen atom form a 5- to 8-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur;

wherein:

R<sup>b</sup> and R<sup>c</sup> are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,

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thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
alkoxycarbonyl, aryloxy carbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
aminosulfonyl wherein the amino nitrogen is (i)  
5 unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
group optionally substituted with one, two or three  
10 groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
two or three groups independently selected from  $R^f$   
substituents;

$R^d$  and  $R^e$  are independently selected from  
15 the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
arylalkylcarbonyl, alkoxy carbonyl and an  
arylalkyloxycarbonyl group; and

$R^f$  is selected from the group consisting of  
20 a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,  
cyano, and a  $R^d R^e$  amino group.

101. The process according to claim 100  
wherein said  $R^1$  is (i) an  $-NR^7R^8$  group in which  $R^7$   
25 and  $R^8$  are independently selected from the group  
consisting of hydrido, hydrocarbyl, aryl, substituted  
aryl, arylhydrocarbyl, and substituted  
arylhydrocarbyl, or (ii)  $R^7$  and  $R^8$  are independently  
selected from the group consisting of a hydrido,  
30 alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl,  
 $R^a$ oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl,  
arylalkyl, heteroaryl, heteroarylalkyl, and a



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heterocyclo substituent, each of which substituent groups is optionally substituted with an -A-R-E-Y substituent;

- in said -A-R-E-Y substituent, A is selected
- 5 from the group consisting of
- (1) -O-;
  - (2) -S-;
  - (3) -NR<sup>k</sup>-;
  - (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
  - 10 (5) -CO-O- or -O-CO-;
  - (6) -O-CO-O-;
  - (7) -HC=CH-;
  - (8) -NH-CO-NH-;
  - (9) -C≡C-;
  - 15 (10) -N=N-;
  - (11) -NH-NH-;
  - (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
  - (13) -CH<sub>2</sub>-;
  - (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
  - 20 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
  - (16) -SO-; and
  - (17) -SO<sub>2</sub>-; or
  - (18) A is absent and R is directly bonded to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;
- 25 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl,
- 30 heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl,

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heteroaryl, cycloalkyl or heterocycloalkyl  
substituent is (i) unsubstituted or (ii) substituted  
with one or two radicals selected from the group  
consisting of a halo, alkyl, perfluoroalkyl,  
5 perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,  
alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,  
hydroxycarbonylalkylamino, nitro, hydroxy,  
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl  
10 group;

the group E is selected from the group  
consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- 15 (3) -CO-;
- (4) -SO<sub>2</sub>R<sup>G</sup>- or -R<sup>G</sup>SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly  
20 to Y; and

the moiety Y is absent or is selected from  
the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
25 heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
30 aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group

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consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
5 (ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group;  
or

R<sup>7</sup> and R<sup>8</sup> taken together with the nitrogen  
atom to which they are bonded form a group -G-A-R-E-Y  
10 wherein

G is a N-heterocyclo group;

the substituent A is selected from the group  
consisting of

- (1) -O-;
- 15 (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- 20 (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- 25 (12) -CS-N(R<sup>k</sup>)- or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- 30 (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded  
to the N-heterocyclo group, G;

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the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, 5 heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl 10 substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, 15 alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the moiety E is selected from the group 20 consisting of

- (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>g</sup>- or -R<sup>g</sup>-SO<sub>2</sub>-;
- 25 (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly to Y; and

the moiety Y is absent or is selected from 30 the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy,

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heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,  
cycloalkyl, trifluoromethyl, alkoxy carbonyl, and a  
5 aminoalkyl group, wherein the aryl, heteroaryl,  
aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
10 haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
(ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group;  
15 wherein R<sup>a</sup> is selected from the group  
consisting of a hydrido, alkyl, alkenyl, alkenyl,  
arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl,  
R<sup>b</sup>R<sup>c</sup>aminoalkanoyl, haloalkanoyl, R<sup>b</sup>R<sup>c</sup>aminoalkyl,  
alkoxyalkyl, haloalkyl and an arylalkyloxy group;  
20 R<sup>g</sup> is selected from the group consisting of  
a hydrido, aryl, heteroaryl, heterocyclo, aroyl,  
alkanoyl, heteroaroyl, halogen cyano, aldehydo,  
hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl,  
cycloalkenyl, alkoxy, aryloxy, heteroaryloxy,  
25 alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  
R<sup>h</sup>R<sup>i</sup>-amino, alkoxyalkyl, alkylendioxy, aryloxyalkyl,  
perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio,  
alkyloxycarbonyl, alkyloxycarbonyloxy,  
aryloxycarbonyl, arylalkyloxycarbonyl,  
30 arylalkyloxycarbonylamino, aryloxycarbonyloxy,  
carboxy, R<sup>h</sup>R<sup>i</sup>-aminocarbonyloxy, R<sup>h</sup>R<sup>i</sup>-aminocarbonyl,  
R<sup>h</sup>R<sup>i</sup>-aminoalkanoyl, hydroxyaminocarbonyl, R<sup>h</sup>R<sup>i</sup>-

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aminosulfonyl,  $R^h R^i$ -aminocarbonyl ( $R^h$ ) amino,  
trifluoromethyl-sulfonyl ( $R^h$ ) amino,  
heteroarylsulfonyl ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) amino,  
arylsulfonyl ( $R^h$ ) aminocarbonyl,  
5 alkylsulfonyl ( $R^h$ ) amino,  
arylcarbonyl ( $R^h$ ) aminosulfonyl, and an  
alkylsulfonyl ( $R^h$ ) aminocarbonyl substituent;

$R^h$  is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
10 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
15 hydroxyalkyl group, each of which groups is  
optionally substituted by one or two groups  
independently selected from  $R^j$  substituents as are  
the substituents of the substituted aminoalkyl and  
substituted aminoalkanoyl groups;

20  $R^i$  is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl,  
substituted or unsubstituted aminoalkyl,  
alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
25 haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
hydroxyalkyl group, each of which groups are  
optionally substituted by one or two  $R^j$  substituents;

$R^j$  is selected from the group consisting of  
30 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,

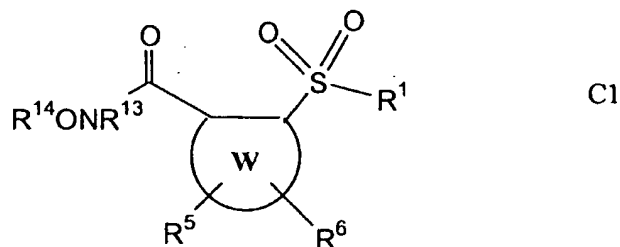
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alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

$R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,  $R^d$ amino carbonyl,  $R^d$ aminosulfonyl,  $R^d$ aminoalkanoyl and  $R^d$ aminoalkysulfonyl.

15

102. The process according to claim 100 wherein said compound corresponds in structure to Formula C1

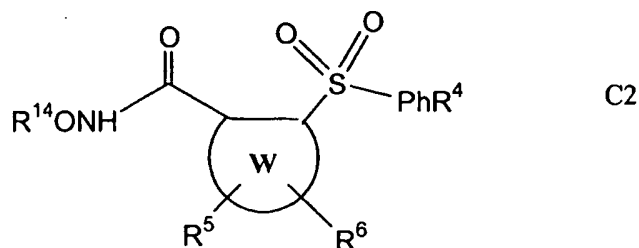


20 wherein W,  $R^1$ ,  $R^5$ ,  $R^6$ ,  $R^{13}$  and  $R^{14}$  are as defined before.

103. The process according to claim 100 wherein said compound corresponds in structure to

25 Formula C2

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wherein W, R<sup>5</sup>, R<sup>6</sup> and R<sup>14</sup> are as defined before, Ph is phenyl substituted at its own 4-

5 position with a substituent R<sup>4</sup>, wherein R<sup>4</sup> is a substituent that has a chain length of 3 to about 14 carbon atoms.

104. The process according to claim 103

10 wherein said R<sup>4</sup> substituent is selected from the group consisting of a phenyl group, a phenoxy group, a thiophenoxy group, an anilino group, a phenylazo group, a phenylureido, a benzamido, a nicotinamido, an isonicotinamido, a picolinamido group, a

15 heterocyclo, heterocyclohydrocarbyl, arylheterocyclohydrocarbyl, arylhydrocarbyl, heteroarylhydrocarbyl, heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl, hydrocarboylhydrocarbyl,

20 arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl, arylazoaryl, arylhydrazinoaryl, hydrocarbylthiohydrocarbyl, hydrocarbylthioaryl, arylthiohydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbylthioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl,

25 arylhydrocarbylthioaryl, arylhydrocarbylamino, heteroarylhydrocarbylamino, and a heteroarylthio group.



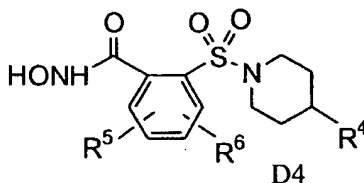
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105. The process according to claim 104 wherein said R<sup>4</sup> substituent is itself substituted by one or more substituents selected from the group consisting of a halogen, hydrocarbyl, hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl, trifluoromethyl-hydrocarbyl, hydroxy, mercapto, hydroxycarbonyl, aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio, heteroarylamino, heteroarhydrocarbyl, hydrocarbyloxycarbonyl-hydrocarbyl, heterocyclooxy, hydroxycarbonyl-hydrocarbyl, heterocyclothio, heterocycloamino, cyclohydrocarbyloxy, cyclohydrocarbylthio, cyclohydrocarbylamino, heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio, heteroarylhydrocarbyl-amino, arylhydrocarbyloxy, arylhydrocarbylthio, arylhydrocarbylamino, heterocyclic, heteroaryl, hydroxycarbonyl-hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarboyloxy, arylhydrocarboyloxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio, hydrocarbyloxyhydrocarbylthio, hydrocarbyloxycarbonyl, hydroxycarbonyl-hydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-hydrocarbylthio, hydrocarbyloxycarbonylhydrocarbyloxy, hydrocarbyloxycarbonylhydrocarbylthio, amino, hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino, heterocyclohydrocarbylcarbonylamino, arylhydrocarbyl-carbonylamino, heteroarylcarbonylamino, heteroarylhydrocarbylcarbonylamino, heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino, arylsulfonylamino, arylhydrocarbylsulfonylamino,

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heteroarylsulfonylamino, heteroarylhydrocarbyl-  
 sulfonylamino, cyclohydrocarbylsulfonylamino,  
 heterocyclohydrocarbylsulfonylamino and N-  
 monosubstituted or N,N-disubstituted aminohydrocarbyl  
 5 group, wherein the substituent(s) on the nitrogen are  
 selected from the group consisting of hydrocarbyl,  
 aryl, arylhydrocarbyl, cyclohydrocarbyl,  
 arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,  
 and hydrocarboyl, or wherein the nitrogen and two  
 10 substituents attached thereto form a 5- to 8-membered  
 heterocyclic or heteroaryl ring group.

106. The process according to claim 100  
 wherein said compound corresponds in structure to  
 15 Formula D4



wherein R<sup>5</sup> and R<sup>6</sup> are as defined before and  
 20 R<sup>4</sup> is a substituent that has a chain length of 3 to  
 about 14 carbon atoms.

107. The process according to claim 106  
 wherein said R<sup>4</sup> substituent is selected from the  
 25 group consisting of a phenyl group, a phenoxy group,  
 a thiophenoxy group, an anilino group, a phenylazo  
 group, a phenylureido, a benzamido, a nicotinamido,  
 an isonicotinamido, a picolinamido group, a  
 heterocyclo, heterocyclohydrocarbyl,

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arylheterocyclohydrocarbyl, arylhydrocarbyl,  
heteroarylhydrocarbyl, heteroarylheterocyclo-  
hydrocarbyl, arylhydrocarbyloxyhydrocarbyl,  
aryloxyhydrocarbyl, hydrocarboylhydrocarbyl,  
5 arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl,  
arylazoaryl, arylhydrazinoaryl, hydrocarbylthio-  
hydrocarbyl, hydrocarbylthioaryl, arylthio-  
hydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbyl-  
thioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl,  
10 arylhydrocarbylthioaryl, arylhydrocarbylamino,  
heteroarylhydrocarbylamino, and a heteroarylthio  
group.

108. The process according to claim 107  
15 wherein said R<sup>4</sup> substituent is itself substituted by  
one or more substituents selected from the group  
consisting of a halogen, hydrocarbyl, hydrocarbyloxy,  
nitro, cyano, perfluorohydrocarbyl, trifluoromethyl-  
hydrocarbyl, hydroxy, mercapto, hydroxycarbonyl,  
20 aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl,  
heteroaryloxy, heteroarylthio, heteroarylamino,  
heteroarhydrocarbyl, hydrocarbyloxycarbonyl-  
hydrocarbyl, heterocyclooxy, hydroxycarbonyl-  
hydrocarbyl, heterocyclothio, heterocycloamino,  
25 cyclohydrocarbyloxy, cyclohydrocarbylthio,  
cyclohydrocarbylamino, heteroarylhydrocarbyloxy,  
heteroarylhydrocarbylthio, heteroarylhydrocarbyl-  
amino, arylhydrocarbyloxy, arylhydrocarbylthio,  
arylhydrocarbylamino, heterocyclic, heteroaryl,  
30 hydroxycarbonyl-hydrocarbyloxy, alkoxycarbonylalkoxy,  
hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl,  
hydrocarboylloxy, arylhydrocarboylloxy,  
hydroxyhydrocarbyl, hydroxyhydrocarbyloxy,

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hydrocarbylthio, hydrocarbyloxyhydrocarbylthio,  
hydrocarbyloxycarbonyl, hydroxycarbonyl-  
hydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl,  
hydrocarbylhydroxycarbonyl-hydrocarbylthio,  
5 hydrocarbyloxycarbonylhydrocarbyloxy,  
hydrocarbyloxycarbonylhydrocarbylthio, amino,  
hydrocarbylcarbonylamino, arylcarbonylamino,  
cyclohydrocarbylcarbonylamino, heterocyclo-  
hydrocarbylcarbonylamino, arylhydrocarbyl-  
10 carbonylamino, heteroarylcarbonylamino,  
heteroarylhydrocarbylcarbonylamino,  
heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,  
arylsulfonylamino, arylhydrocarbylsulfonylamino,  
heteroarylsulfonylamino, heteroarylhydrocarbyl-  
15 sulfonylamino, cyclohydrocarbylsulfonylamino,  
heterocyclohydrocarbylsulfonylamino and N-  
monosubstituted or N,N-disubstituted aminohydrocarbyl  
group, wherein the substituent(s) on the nitrogen are  
selected from the group consisting of hydrocarbyl,  
20 aryl, arylhydrocarbyl, cyclohydrocarbyl,  
arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,  
and hydrocarboyl, or wherein the nitrogen and two  
substituents attached thereto form a 5- to 8-membered  
heterocyclic or heteroaryl ring group.

25

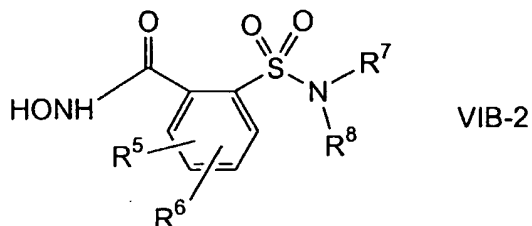
109. The process according to claim 100  
wherein said R<sup>1</sup> substituent has a length greater than  
that of an octyl group and less than that of a  
stearyl group.

30

110. The process according to claim 100  
wherein said compound or salt is administered a  
plurality of times.

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111. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that comprises
- 5 administering a compound corresponding in structure to Formula VIB-2 or a pharmaceutically acceptable salt thereof in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition:



10

wherein

- R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy,
- 15 haloalkyl, haloalkyloxy, hydroxyalkyl, a R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocyclooxy and a R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

- 20 or R<sup>5</sup> and R<sup>6</sup> together with the atoms to which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members; and

- said R<sup>7</sup> and R<sup>8</sup> are independently selected
- 25 from the group consisting of a hydrido, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, R<sup>a</sup>oxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and a heterocyclo

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substituent, each of which substituent groups is optionally substituted with an -A-R-E-Y substituent; in said -A-R-E-Y substituent, A is selected from the group consisting of

- 5 (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- 10 (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -N=N-;
- 15 (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>) - or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- 20 (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to R<sup>7</sup> or R<sup>8</sup>, or both R<sup>7</sup> and R<sup>8</sup>;

the moiety R is selected from the group

25 consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl,

30 heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl

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- substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;
- the group E is selected from the group consisting of
- (1) -COR<sup>g</sup>- or -R<sup>g</sup>CO-;
  - (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
  - (3) -CO-;
  - (4) -SO<sub>2</sub>R<sup>g</sup>- or -R<sup>g</sup>SO<sub>2</sub>-;
  - (5) -SO<sub>2</sub>-;
  - (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
  - (7) E is absent and R is bonded directly to Y; and
- Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, and an amino

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group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group; or

5                     $R^7$  and  $R^8$  taken together with the nitrogen atom to which they are bonded form a group -G-A-R-E-Y wherein

G is a N-heterocyclo group;

the substituent A is selected from the

10 group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- 15 (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- 20 (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- 25 (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and
- (17) -SO<sub>2</sub>-; or
- (18) A is absent and R is directly bonded to the N-heterocyclo group, G;
- 30 the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl,



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heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl,  
heterocycloalkoxyalkyl, aryloxyalkyl,  
heteroaryloxyalkyl, arylthioalkyl,  
heteroarylthioalkyl, cycloalkylthioalkyl, and a  
5 heterocycloalkylthioalkyl group wherein the aryl or  
heteroaryl or cycloalkyl or heterocycloalkyl  
substituent is (i) unsubstituted or (ii) substituted  
with one or two radicals selected from the group  
consisting of a halo, alkyl, perfluoroalkyl,  
10 perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,  
alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl,  
hydroxycarbonylalkylamino, nitro, hydroxy,  
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl  
15 group;

the moiety E is selected from the group  
consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- 20 (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>G</sup>- or -R<sup>G</sup>-SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- (7) E is absent and R is bonded directly  
25 to Y; and

the moiety Y is absent or is selected from  
the group consisting of a hydrido, alkyl, alkoxy,  
haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl,  
hydroxy, nitrile, nitro, aryloxy, aralkoxy,  
30 heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl,  
perfluoroalkoxy, perfluoroalkylthio,  
trifluoromethylalkyl, alkenyl, heterocycloalkyl,

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cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a  
aminoalkyl group, wherein the aryl, heteroaryl,  
aralkyl or heterocycloalkyl group is (i)  
unsubstituted or (ii) substituted with one or two  
5 radicals independently selected from the group  
consisting of an alkanoyl, halo, nitro, nitrile,  
haloalkyl, alkyl, aralkyl, aryl, alkoxy,  
perfluoroalkyl, perfluoroalkoxy and an amino group  
wherein the amino nitrogen is (i) unsubstituted or  
10 (ii) substituted with one or two groups independently  
selected from hydrido, alkyl, and an aralkyl group;

$R^a$  is selected from the group consisting of  
a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl,  
alkanoyl, aroyl, arylalkylcarbonyl,  $R^bR^c$ aminoalkanoyl,  
15 haloalkanoyl,  $R^bR^c$ aminoalkyl, alkoxyalkyl, haloalkyl  
and an arylalkyloxy group;

$R^b$  and  $R^c$  are independently selected from  
the group consisting of a hydrido, alkanoyl,  
arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl,  
20 perfluoroalkyl, trifluoromethylalkyl,  
perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl,  
heterocycloalkyl, heterocycloalkylcarbonyl, aryl,  
heterocyclo, heteroaryl, cycloalkylalkyl,  
aryloxyalkyl, heteroaryloxyalkyl,  
25 heteroarylalkoxyalkyl, heteroarylthioalkyl,  
arylsulfonyl, aralkanoyl, alkylsulfonyl,  
heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
alkyliminocarbonyl, aryliminocarbonyl,  
30 heterocycloiminocarbonyl, arylthioalkyl,  
alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,

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alkoxycarbonyl, aryloxy carbonyl, aminoalkyl carbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, aminosulfonyl wherein the amino nitrogen is (i) unsubstituted or (ii) independently substituted with one or two  $R^d$  radicals, or the substituents on the amino group taken together with the amino nitrogen form a saturated or partially unsaturated heterocyclo group optionally substituted with one, two or three groups independently selected from  $R^d$  substituents or a heteroaryl group optionally substituted with one, two or three groups independently selected from  $R^f$  substituents;

$R^d$  and  $R^e$  are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkyl carbonyl, alkoxycarbonyl and an arylalkyloxycarbonyl group; and

$R^f$  is selected from the group consisting of a nitro, hydroxy, alkyl, halogen, aryl, alkoxy, cyano, and a  $R^d R^e$  amino group;

$R^g$  is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  $R^{hRi}$ -amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxy-carbonyl, arylalkyloxycarbonyl, arylalkyloxy-carbonylamino, aryloxycarbonyloxy, carboxy,  $R^{hRi}$ -aminocarbonyloxy,  $R^{hRi}$ -aminocarbonyl,  $R^{hRi}$ -

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aminoalkanoyl, hydroxyaminocarbonyl,  $R^h R^i$ -aminosulfonyl,  $R^h R^i$ -aminocarbonyl ( $R^h$ ) amino, trifluoromethylsulfonyl ( $R^h$ ) amino, heteroarylsulfonyl- ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) amino, arylsulfonyl ( $R^h$ ) -  
5 aminocarbonyl, alkylsulfonyl ( $R^h$ ) amino, arylcarbonyl- ( $R^h$ ) aminosulfonyl, and an alkylsulfonyl ( $R^h$ ) -aminocarbonyl substituent;

$R^h$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
10 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a  
15 hydroxyalkyl group, each of which groups is optionally substituted by one or two groups independently selected from  $R^j$  substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

20  $R^i$  is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
25 haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two  $R^j$  substituents;

$R^j$  is selected from the group consisting of  
30 an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl,

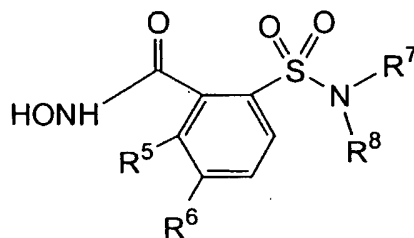
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alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

$R^k$  is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl,  $R^{CR^d}$ amino carbonyl,  $R^{CR^d}$ aminosulfonyl,  $R^{CR^d}$ aminoalkanoyl and  $R^{CR^d}$ aminoalkysulfonyl.

15

112. The process according to claim 111 wherein said compound corresponds in structure to Formula VIB-3



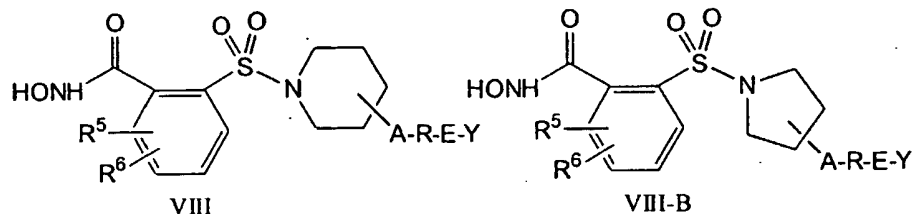
VIB-3

20

113. The process according to claim 111 wherein said compound corresponds in structure to Formula VIII or VIII-B

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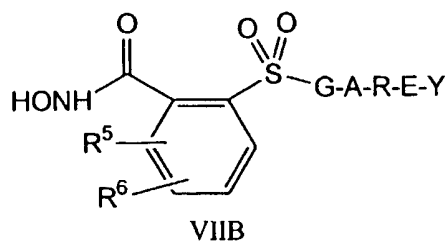


114. The process according to claim 111 wherein said  $\text{NR}^7\text{R}^8$  substituent has a length greater than that of an octyl group and less than that of a stearyl group.

115. The process according to claim 114 wherein said  $\text{NR}^7\text{R}^8$  is the substituent -G-A-R-E-Y.

116. The process according to claim 111 wherein said compound or salt is administered a plurality of times.

117. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that comprises administering a compound corresponding in structure to Formula VIIB or a pharmaceutically acceptable salt thereof in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition:



wherein

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R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of a hydrido, alkyl, cycloalkyl, acylalkyl, halo, nitro, hydroxyl, cyano, alkoxy, haloalkyl, haloalkyloxy, hydroxyalkyl, a

5 R<sup>b</sup>R<sup>c</sup>aminoalkyl substituent, thiol, alkylthio, arylthio, cycloalkylthio, cycloalkoxy, alkoxyalkoxy, perfluoroalkyl, haloalkyl, heterocycloxy and a R<sup>b</sup>R<sup>c</sup>aminoalkyloxy substituent;

or R<sup>5</sup> and R<sup>6</sup> together with the atoms to  
10 which they are bonded form a further aliphatic or aromatic carbocyclic or heterocyclic ring having 5- to 7-members; and

in the substituent -G-A-R-E-Y, G is a N-heterocyclo group;

15 the substituent A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- 20 (4) -CO-N(R<sup>k</sup>) or -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- 25 (9) -C≡C-;
- (10) -N=N-;
- (11) -NH-NH-;
- (12) -CS-N(R<sup>k</sup>) - or -N(R<sup>k</sup>)-CS-;
- (13) -CH<sub>2</sub>-;
- 30 (14) -O-CH<sub>2</sub>- or -CH<sub>2</sub>-O-;
- (15) -S-CH<sub>2</sub>- or -CH<sub>2</sub>-S-;
- (16) -SO-; and

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(17) -SO<sub>2</sub>-; or

(18) A is absent and R is directly bonded to the N-heterocyclo group, G;

the moiety R is selected from the group

- 5 consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group
- 15 consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy,
- 20 hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the moiety E is selected from the group consisting of

- (1) -COR<sup>G</sup>- or -R<sup>G</sup>CO-;
- 25 (2) -CON(R<sup>k</sup>)- or -(R<sup>k</sup>)NCO-;
- (3) -CO-;
- (4) -SO<sub>2</sub>-R<sup>G</sup>- or -R<sup>G</sup>-SO<sub>2</sub>-;
- (5) -SO<sub>2</sub>-;
- (6) -N(R<sup>k</sup>)-SO<sub>2</sub>- or -SO<sub>2</sub>-N(R<sup>k</sup>)-; or
- 30 (7) E is absent and R is bonded directly to Y; and



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the moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy,

- 5 heteroaryloxy, heteroaralkyl, R<sup>a</sup>oxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and an aminoalkyl group, wherein the aryl, heteroaryl, aralkyl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, perfluoroalkyl, perfluoroalkoxy and an amino group
- 10 wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group;

- wherein R<sup>a</sup> is selected from the group consisting of a hydrido, alkyl, alkenyl, alkenyl, arylalkyl, aryl, alkanoyl, aroyl, arylalkylcarbonyl, R<sup>b</sup>R<sup>c</sup>aminoalkanoyl, haloalkanoyl, R<sup>b</sup>R<sup>c</sup>aminoalkyl, alkoxyalkyl, haloalkyl and an arylalkyloxy group;
- 20

- R<sup>b</sup> and R<sup>c</sup> are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, aralkanoyl, alkylsulfonyl,
- 25
- 30

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- heteroarylsulfonyl, carboxyalkyl,  
alkoxycarbonylalkyl, aminocarbonyl,  
alkyliminocarbonyl, aryliminocarbonyl,  
heterocycloiminocarbonyl, arylthioalkyl,  
5 alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl,  
heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl,  
thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl,  
alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl,  
hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl,  
10 aminosulfonyl wherein the amino nitrogen is (i)  
unsubstituted or (ii) independently substituted with  
one or two  $R^d$  radicals, or the substituents on the  
amino group taken together with the amino nitrogen  
form a saturated or partially unsaturated heterocyclo  
15 group optionally substituted with one, two or three  
groups independently selected from  $R^d$  substituents or  
a heteroaryl group optionally substituted with one,  
two or three groups independently selected from  $R^f$   
substituents;  
20  $R^d$  and  $R^e$  are independently selected from  
the group consisting of a hydrido, alkyl, alkenyl,  
alkenyl, arylalkyl, aryl, alkanoyl, aroyl,  
arylalkylcarbonyl, alkoxycarbonyl and an  
arylalkyloxycarbonyl group; and  
25  $R^f$  is selected from the group consisting of  
a nitro, hydroxy, alkyl, halogen, aryl, alkoxy,  
cyano, and a  $R^d R^e$  amino group;  
 $R^g$  is selected from the group consisting of  
a hydrido, aryl, heteroaryl, heterocyclo, aroyl,  
30 alkanoyl, heteroaroyl, halogen cyano, aldehydo,  
hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl,  
cycloalkenyl, alkoxy, aryloxy, heteroaryloxy,

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- alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl,  
R<sup>h</sup>R<sup>i</sup>-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl,  
perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio,  
alkyloxycarbonyl, alkyloxycarbonyloxy,  
5 aryloxycarbonyl, arylalkyloxycarbonyl,  
arylalkyloxycarbonylamino, aryloxycarbonyloxy,  
carboxy, R<sup>h</sup>R<sup>i</sup>-aminocarbonyloxy, R<sup>h</sup>R<sup>i</sup>-aminocarbonyl,  
R<sup>h</sup>R<sup>i</sup>-aminoalkanoyl, hydroxyaminocarbonyl, R<sup>h</sup>R<sup>i</sup>-  
aminosulfonyl, R<sup>h</sup>R<sup>i</sup>-aminocarbonyl(R<sup>h</sup>)amino,  
10 trifluoromethyl-sulfonyl(R<sup>h</sup>)amino,  
heteroarylsulfonyl(R<sup>h</sup>)amino, arylsulfonyl(R<sup>h</sup>)amino,  
arylsulfonyl(R<sup>h</sup>)aminocarbonyl,  
alkylsulfonyl(R<sup>h</sup>)amino,  
arylcarbonyl(R<sup>h</sup>)aminosulfonyl, and an  
15 alkylsulfonyl(R<sup>h</sup>)aminocarbonyl substituent;

- R<sup>h</sup> is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl,  
substituted or unsubstituted aminoalkyl,  
20 alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl,  
haloalkyl, alkanoyl, aroyl, substituted or  
unsubstituted aminoalkanoyl, halo alkanoyl and a  
hydroxyalkyl group, each of which groups is  
optionally substituted by one or two groups  
25 independently selected from R<sup>j</sup> substituents as are  
the substituents of the substituted aminoalkyl and  
substituted aminoalkanoyl groups;

- R<sup>i</sup> is selected from the group consisting of  
an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl,  
30 alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl,  
substituted or unsubstituted aminoalkyl,

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alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are

5 optionally substituted by one or two R<sup>j</sup> substituents;

R<sup>j</sup> is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl,

10 alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl  
15 groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group; and

R<sup>k</sup> is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R<sup>C</sup>R<sup>d</sup>amino carbonyl, R<sup>C</sup>R<sup>d</sup>aminosulfonyl, R<sup>C</sup>R<sup>d</sup>aminoalkanoyl and R<sup>C</sup>R<sup>d</sup>aminoalkysulfonyl.

25 118. The process according to claim 117 wherein said compound or salt is administered a plurality of times.

## INTERNATIONAL SEARCH REPORT

Inter~~national~~ Application No

PCT/US 00/06713

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/16 C07C317/44 C07C311/21 C07C311/16 C07D207/14  
 C07D211/46 C07D211/18 C07D401/12 C07D211/54 C07D295/22  
 C07D401/04 C07D405/12 C07D409/12 C07D405/14 C07D309/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 38859 A (MCDONALD JOSEPH J ; MONSANTO CO (US); BARTA THOMAS E (US); BECKER D) 11 September 1998 (1998-09-11)  comparative examples 3,4,7,8; page 111, table 38  ----	1-5,7-9, 15,22, 23,31, 32,100
X	WO 98 06705 A (BROWN GEORGE ROBERT ; WATERSON DAVID (GB); ZENECA LTD (GB); NEWCOMB) 19 February 1998 (1998-02-19) page 30, compound no 34  ----	1,23
E	WO 00 37107 A (MASFERRER JAIME L ; GORDON GARY (US); SEARLE & CO (US); KOKI ALANE) 29 June 2000 (2000-06-29)  examples  -----	1,15,22, 23,31, 32,100, 111,117

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

30 August 2000

Date of mailing of the international search report

12/09/2000

Name and mailing address of the ISA

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Authorized officer

De Jong, B

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/06713

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D401/14 A61K31/16 A61K31/445 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,14,23-25,30,100,101,109,110, (all partially)

Present claims 1-4,23-25,30,100,101,109,110 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to claims 5-13,15-22,26-29,31-99,102-108,111-118

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/06713

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